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Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R01NS090645

Title: 'Gadding' about the brain: Understanding the function of GABAergic signaling during neural development in larval zebrafish

Authors: *A. J. VANLEUVEN[1], R. E. BALL[1], J. B. BYERS[1], Y. LIU[2], P. KNER[2], A. T. SORNBORGER[3], J. D. LAUDERDALE[1]
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Abstract: Normal nervous system development and function requires a fine balance of excitatory and inhibitory activity. Γ-Aminobutyric Acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system of all vertebrates. GABA is made by the glutamic acid decarboxylase (GAD) enzyme, which exists in two isoforms, GAD67 and GAD65. The genes *Gad1* and *Gad2* encode these isoforms, respectively, and both function in GABA synthesis. Like mammals, zebrafish have both known *gad* genes; however, our lab has recently found evidence for a *gad1* paralog in zebrafish. These three *gad* isoforms in the zebrafish exhibit differential spatial and temporal expression, particularly in the developing spinal cord. These observed differences in *gad* expression have interesting implications both in terms of neural development and in nervous system function. To further investigate the function of the *gad* genes and to elucidate the role of GABA signaling during development, we are using CRISPR/Cas9 for targeted mutagenesis. We have made novel alleles for all three of the *gad* genes in zebrafish using CRISPR/Cas9 to address the question of how genetic manipulations in GABAergic signaling affect neural development and neurological activity. So far we have shown that *gad1b* -/- mutant zebrafish have increased and abnormal brain activity in electrophysiological recordings as compared to wild-type animals. We are currently testing the *gad1a* and *gad2* mutant zebrafish for neurological and/or developmental differences. Additionally, we are using these mutant zebrafish in conjunction with transgenic zebrafish, calcium imaging, and light sheet microscopy to better understand the connectivity and activity of inhibitory neural networks when GABAergic signaling is altered *in vivo*. These experiments will aid our understanding of the differential regulation of GABA synthesis and the fine-tuning of the central nervous system's inhibitory network during development.

Disclosures: **A.J. Vanleuven:** None. **R.E. Ball:** None. **J.B. Byers:** None. **Y. Liu:** None. **P. Kner:** None. **A.T. Sornborger:** None. **J.D. Lauderdale:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: EPSRC Grant (EP/K026992/1)

MRC Grant (MR/N015037/1)

Title: Computational modeling of layer formation in cortex using apoptosis

Authors: *R. BAUER[1,2], M. KAISER[2,1]
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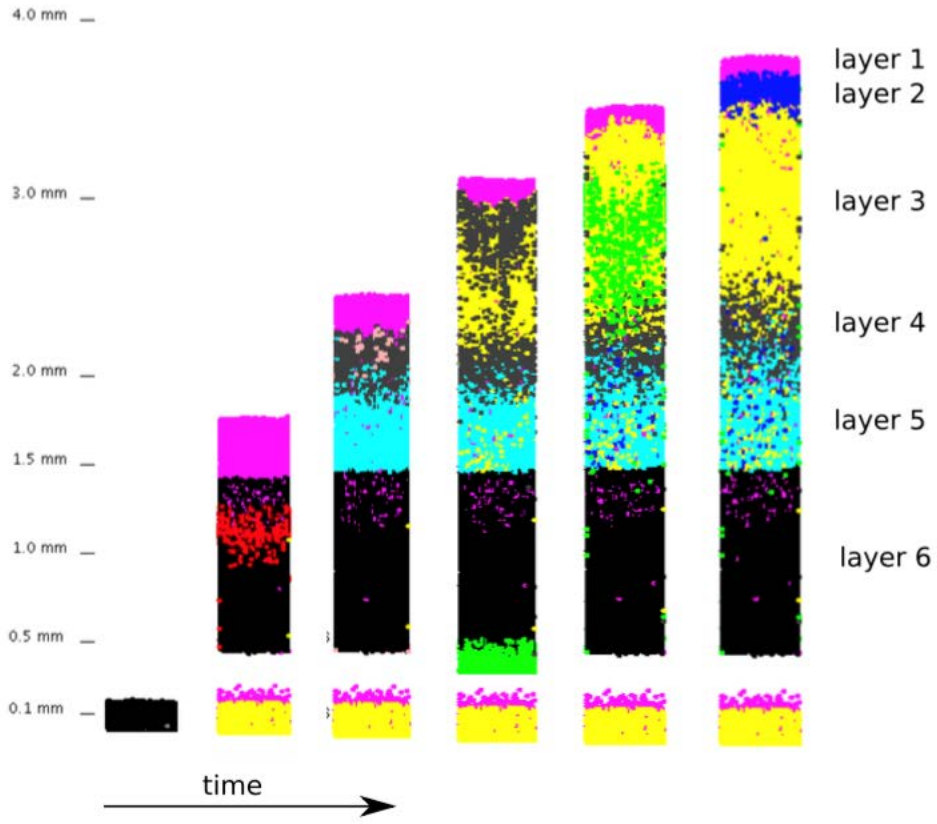
Abstract: One of the most characteristic properties of mammalian neural systems is the presence of a layered structure comprising different cell types. This architecture exists in cortex, in the retina, in the hippocampus and many other parts of the central nervous system (CNS). The developmental origin of this common architecture has been the research focus of substantial experimental efforts. However, only few studies provide a quantitative or computational framework for neural layer formation.
Here, we devise a detailed and mechanistic computational model of cortical layer formation. Starting from a small pool of undifferentiated precursor cells, the development of a layered cortex in 3D physical space is simulated (see figure). This agent-based model is a composition of a small number of fundamental mechanisms of biology, such as cell proliferation, differentiation, migration and diffusion of chemicals in extracellular space. The temporal coordination of these behaviors is specified through a gene regulatory network model that is instantiated within each cell. The state of each cell is dynamically determined by the interaction of intracellular as well as extracellular processes.
Our results show how the characteristic inside-out development of cortical layer formation can be accounted for. In particular, we show that apoptosis strongly improves the layer architecture, and enables a wide range of layer thicknesses as measured in human and mouse cortex. Importantly, this improvement is accomplished via two distinct apoptotic processes that require different kinds of feedback. The model complexity is reduced due to the presence of repetitions of similar behaviors.
Overall, we provide a biologically plausible, mechanistic model of layer formation. Our results suggest a crucial function for apoptosis during the development of cell layers in the CNS. Moreover, certain features of neurodevelopmental disorders can be accounted for by changes to the gene-type rules of our model, which gives rise to novel hypotheses on the origins of these disorders.



Disclosures: **R. Bauer:** None. **M. Kaiser:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant P0512278 (OY)

NIH Grant MH77694 (SP)

Title: Investigating the roles of Sonic Hedgehog signaling in the establishment of postnatal neural stem cells from embryonic cortical progenitors

Authors: H. GOMEZ, J. GARCIA, D. AGUILAR, S. PLEASURE, *O. R. YABUT
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Abstract: Neural stem cells (NSCs) in the postnatal ventricular-subventricular zone (V-SVZ) originate from discrete germinal regions of the embryonic forebrain. Furthermore, the spatial localization of progenitors in the pallium and the subpallium dictate the regional positioning of postnatal NSCs in the cortical, striatal, and septal walls of the V-SVZ, thereby influencing the generation of specific interneuron lineages that migrate to the olfactory bulb (OB). However, the molecular mechanisms that direct the specification of postnatal NSCs from embryonic progenitors are still incompletely understood. We are now investigating whether the activity of Sonic Hedgehog signaling (Shh) in the embryonic mammalian brain specifically play a role in this process. Our recent studies showed that ectopic activation of Shh signaling in the embryonic neocortex, achieved by conditional deletion of the Shh inhibitor Suppressor of Fused (Sufu) using the hGFAP-Cre driver (hGFAP-Cre/+;Sufu-fl/fl), results in the abnormal proliferation and specification of cortical progenitors at a time when postnatal NSCs are specified. Thus, we wondered whether the ability of these progenitors to generate NSCs that eventually populate the postnatal V-SVZ is similarly perturbed. Indeed, hGFAP-Cre/+;Sufu-fl/fl mice exhibit a dramatic expansion of DCX+ neuroblasts at postnatal day (P) 7, indicating abnormal proliferation of NSCs. This is coupled with an increase in apoptotic cells in the V-SVZ, which prompted ongoing investigation on whether these neuroblasts are able to generate functional interneurons in the OB. Preliminary studies also reveal that deactivation of Sufu in embryonic cortical progenitors lead to the abnormal expression/activity of previously reported regulators of NSCs in the V-SVZ. These results imply that modulation of Shh signaling at embryonic stages could be critical in maintaining specific NSC populations in the postnatal V-SVZ.

Disclosures: H. Gomez: None. **J. Garcia:** None. **D. Aguilar:** None. **S. Pleasure:** None. **O.R. Yabut:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01 NS092339

NIH Grant R01 NS085081

Title: Sox9-expressing neural stem cells in the neocortex generate neurons of all cortical layers

Authors: *E. S. KAPLAN, K. A. RAMOS-LAGUNA, A. B. MIHALAS, R. A. M. DAZA, R. F. HEVNER
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Abstract: The mammalian cerebral cortex is a highly organized structure, which contains layers of neurons that share similar properties including gene expression and connectivity patterns. The formation of this laminar structure occurs as neural progenitors differentiate into post-mitotic neurons, which in turn migrate radially to occupy their final positions. Abundant research suggests that neural progenitors become progressively restricted in their competency to produce neurons of different cortical layers. That is, progenitors earlier in development can give rise to neurons of any cortical layer, while later progenitors can give rise only to upper layer neurons. However, this classic model has been challenged by the idea that certain populations of progenitors may be inherently restricted and programmed to produce neurons fated for particular lamina. Considering that the existence of fate-restricted progenitors remains hotly debated; it is clear that additional tools affording the capacity to monitor neural progenitor lineages are needed to support or refute the classic model. Here, we utilize inducible genetic fate mapping and clonal analysis of early Sox9+ cortical progenitors and their descendants. We find that Sox9-expressing neural progenitors give rise to neurons of all cortical layers, and find no evidence to support laminar fate-restricted progenitor lineages.

Disclosures: E.S. Kaplan: None. **K.A. Ramos-Laguna:** None. **A.B. Mihalas:** None. **R.A.M. Daza:** None. **R.F. Hevner:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: SFN-IBRO Travel Award

Title: Post-transcriptional regulation of mir-3099 during neurogenesis

Authors: *S. ZAINAL ABIDIN[1,4], F. SZE ZHENG[2,4], N. NORDIN[2], S. ABDULLAH[2], C. PIKE SEE[3,4], L. KING HWA[2,4]
[2]Biomed. Sci., [3]Anat., [1]Universiti Putra Malaysia, Serdang, Malaysia; [4]NeuroBiology and Genet. Group, Universiti Putra Malaysia, Malaysia

Abstract: In 2011, *miR-3099* was discovered through the deep sequencing of RNA isolated from the E15.5 developing mouse brain. *MiR-3099* was previously found highly expressed throughout embryogenesis and localised in cortical plate between E13.5 and E17.5 in developing mouse brain. Majority of the cell in the brain at these time-points are committed to neuronal cell lineage. To understand more on the role of *miR*-3099 during neurogenesis, this study aims to characterise the functional role of *miR-3099* via ‘gain-of-function’ study. To relate the role of *miR-3099* to neurogenesis, neuronal development and function, *miR-3099* was overexpressed at

different time-points during the transition or development of mouse embryonic stem (mES) cells to neural precursor stem cells (NPCs) and neurones (mES-NPC-neurones). Then, to ascertain the differential phenotypic changes between induced and uninduced cell, specific marker such as Oct4, Sox1, Tuj1 and Gfap was analysed using immunocytochemistry (ICC) techniques, flow-cytometric and RT-qPCR. Three housekeeping genes, *Hmbs*, *Psmb2* and *Pgk1*, was used to normalise all qualitative and quantitative RT-PCR analysis performed. In addition, the expression level of *miR-3099* was evaluated using pulsed-stem-loop RT-qPCR and normalised using *U6* gene. This finding would lead to a better understanding of its role during neuronal cell development and function, thus providing a model to understand the development of the mammalian brain.
Keywords: *miR-3099*, gliogenesis, neurogenesis, neuronal, astrocyte

Disclosures: **S. Zainal Abidin:** None. **F. Sze Zheng:** None. **N. Nordin:** None. **S. Abdullah:** None. **C. Pike See:** None. **L. King Hwa:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant

Title: ARX suppresses ventral fate in the dorsal forebrain through modulation of SHH, FGF, and WNT signaling

Authors: ***G. CHO**[1], Y. LIM[1], I. CHO[1], X. SHI[1], J. B. GRINSPAN[2], J. A. GOLDEN[1]
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Abstract: Early brain development requires an intricate orchestration between patterning and growth of the neural tube. Yet, how pattern formation and the control of brain size are coordinated during development is not well understood. The Aristaless-related homeobox (ARX) transcription factor has been shown to regulate cortical progenitor pool expansion, thus the size of the cortex, by repressing an inhibitor of cell cycle progression. Here we report that ARX also controls the dorsal identity of the mouse forebrain by suppressing ventral identity in the dorsal forebrain. Loss of ARX leads to the overexpression of ventrally restricted genes, including *Olig2*, in dorsal domains, as the result of perturbed SHH, FGF, and WNT signaling. We further show that the resulting overexpression of *Olig2* in $Arx^{-/y}$ mice results in the repression of *Pax6* and *Tbr2* expression, dorsal specific genes crucial for normal proliferation and/or differentiation of cortical progenitor cells. Our findings suggest that ARX modulates multiple signaling

pathways for specification of dorsal progenitors, and that it serves as a transcription factor integrating normal forebrain patterning and growth.

Disclosures: G. Cho: None. **Y. Lim:** None. **I. Cho:** None. **X. Shi:** None. **J.B. Grinspan:** None. **J.A. Golden:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: R01AA024659

Title: Intracellular calcium dynamics in fetal neural progenitors after ethanol exposure and withdrawal

Authors: *A. H. MAHNKE, R. C. MIRANDA
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Abstract: Ethanol is a known teratogen and *in utero* exposure can lead to neurodevelopmental, behavioral, and cognitive disorders known collectively as Fetal Alcohol Spectrum Disorders. The end of the first trimester to the beginning of the second trimester is a particularly sensitive time to ethanol exposure, since during this time stem cells rapidly divide to produce most of the adult neurons. Previously, we showed that ethanol exposure during this period alters the programming of murine neural stem cells to favor premature maturation, to the decrement of self-renewal. Here, we further examine how ethanol exposure at moderate, binge-like, and excessive chronic drinking levels (60mg/dL, 120mg/dL, and 320mg/dL) affects active cellular dynamics in neural progenitor cells. Cultures of gestational day 12.5-derived, C57BL/6 mouse neural stem cells, maintained as non-adherent neurospheres, were exposed to ethanol for five days and subsequently loaded with Fluo-4AM. Intracellular calcium dynamics were imaged using confocal microscopy. An additional set of neurospheres were withdrawn from ethanol for an additional two days before imaging. Cells within an individual neurosphere are heterogeneous with respect to calcium dynamics in that some cells maintain steady calcium levels, while other cells exhibit dynamic calcium activity. Chronic treatment with ethanol affected the resting calcium levels and calcium event dynamics in a dose-dependent manner. Moreover, the 120mg/dL and 320mg/dL had lasting effects on calcium dynamics which persisted even after two days of withdrawal. Chronic ethanol exposure also blunted the calcium response to acute, moderate and binge-like dose, ethanol exposures, as well as to nicotine and ethanol co-administration. Preliminary evidence shows that topological analysis of these neurospheres can lead to the identification of cellular populations within the neurosphere based on calcium

dynamics throughout the imaging period. These data firstly indicate the emergence of significant and surprising cell-to-cell variability in calcium activity among daughter fetal neural progenitors within a neurosphere niche that originate from a common stem cell. These data also show that ethanol exposure continues to perturb cellular dynamics even after ethanol is withdrawn, which may contribute to prolonged alterations to calcium-dependent intracellular signaling pathways that control neural stem cell growth and maturation.

Disclosures: A.H. Mahnke: None. **R.C. Miranda:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: AA024659

Title: Teratogen-sensitive exosomal miRNAs control the growth and maturation of fetal neural progenitors

Authors: *D. CHUNG[1], A. TSENG[3], S. EAVES[2], N. A. SALEM[4], A. H. MAHNKE[4], R. C. MIRANDA[5]
[1]Neurosci. and Exptl. Therapeut., Texas A&M Univ., bryan, TX; [2]Texas A&M Univ., College Station, TX; [3]Mol. & Cell. Med., Texas A&M Hlth. Sci. Ctr., College Station, TX; [4]Neurosci. and Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr., Bryan, TX; [5]Neurosci. & Exptl. Therapeut., Texas A&M Hlth. Sci. Ctr, Col. of Med., Bryan, TX

Abstract: Prenatal alcohol exposure can result in craniofacial abnormalities, growth deficits, and is the leading cause of neurodevelopment disability worldwide. Neural stem cells (NSCs) are particularly vulnerable to alcohol (ethanol) exposure during the late first through the second trimester, when they are most extensively involved in neurogenesis. NSCs reside in a complex microenvironment rich in exosomes, a class of microvesicles shown to traffic protein, lipid, and RNA cargo between cells. Ethanol exposure resulted in a significant elevation in the levels of a subset of miRNAs in exosomes. Overexpression studies showed that two of the elevated miRNAs including miR-140-3p, a miRNA we have previously shown to be both nicotine and alcohol sensitive, increased neurosphere growth. Overexpression of both miR-140-3p and miR-140-5p significantly increased the proportion of S-phase cells while decreasing the proportion of G_0/G_1 cells compared to controls. In contrast, while miR-140-3p and miR-140-5p knockdown did not produce a discernible effect on the proportion of cells in each phase of the cell cycle, it did significantly decrease the rate of DNA synthesis. Collectively, our results suggest that mir-140 influences cell cycle kinetics. Furthermore, miR-140-3p overexpression during in vitro

mitogen-withdrawal induced NSC differentiation, favored glial fate, at the expense of neural and oligodendroglial differentiation. Therefore, the dysregulated miRNA content of exosomes following ethanol exposure may result in aberrant neural progenitor cell growth and maturation and explain brain growth deficits associated with prenatal alcohol exposure.

Disclosures: D. Chung: None. **A. Tseng:** None. **S. Eaves:** None. **N.A. Salem:** None. **A.H. Mahnke:** None. **R.C. Miranda:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Title: Analysis of epigenetic factors in human neural stem cells exposed to high glucose

Authors: *D. KANDILYA[1], A. BANIK[1], W. STÜNKEL[3], Y. S. CHONG[2], S. T. DHEEN[1]
[1]Anat., Natl. Univ. of Singapore, singapore, Singapore; [2]Dept. of Obstetrics and Gynaecology, Natl. Univ. of Singapore, Singapore, Singapore; [3]Singapore Inst. for Clin. Sci., Agency for Sci. and Technol. Res. (A*STAR), Singapore, Singapore

Abstract: Gestational diabetes mellitus (GDM) has been shown to induce neurodevelopmental and cognitive impairments in offspring. Recently, an animal model study showed that hyperglycemia during pregnancy alters the expression pattern of genes involved in neurogenesis and gliogenesis in developing brain of the fetus. It is hypothesized that GDM alters the epigenetic mechanisms such as DNA methylation and histone modifications that regulate the expression of genes critical for brain development. In the present study, global DNA methylation and histone modifications were found to be altered in human neural stem cell line (hNSCs) exposed to high glucose. The high throughput DNA methylation studies using MethylEPIC array which scans methylation over 850,000 CpG islands revealed that the genes involved in neurodevelopmental and axon guidance pathway were found to exhibit altered methylation pattern in hNSCs exposed to high glucose.One of the genes that show altered methylation in hNSCs exposed to high glucose was Slit1 which binds with its receptor Robo and contributes to axon repulsion, critical for brain development. Slit-1 has been found to be hypomethylated and its expression was up-regulated in hNSCs exposed to high glucose. These results suggest that high glucose concentration alters the Slit-Robo signaling pathway in hNSCs, thereby resulting in impaired axon guidance and brain patterning. In addition, high glucose-induced histone modifications in hNSCs were detected using a histone H3 array and in particular, H3K56ac and H3K14ac, a hallmark of gene activation, were found to be significantly up-regulated. Taken together these data suggest that genome-wide modifications of DNA methylation and histone

acetylation (i.e. H3K56 and H3K14) in hNSCs exposed to high glucose provide a basis for altered expression of genes critical for neurodevelopment.

Disclosures: D. Kandilya: None. **A. Banik:** None. **W. Stünkel:** None. **Y.S. Chong:** None. **S.T. Dheen:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Title: Regulation of cortical development by anaplastic lymphoma kinase

Authors: *R. MAO[1], G. WANG[1], R. DENG[1], Z. JIA[2], Z. ZHOU[1]
[1]Inst. of Life Sciences, Southeast Univ., Jiangsu, China; [2]Neurosciences and Mental Health, The Hosp. for Sick Children, Dept. of Physiol., Univ. of Toronto, Toronto, ON, Canada

Abstract: Anaplastic lymphoma kinase (*Alk*) is a receptor-type protein tyrosine kinase that is transiently and specifically expressed in the nervous systems during embryonic stages. Studies in Drosophila, Caenorhabditis elegans and mice have reported that Alk signaling plays important role in learning and neurogenesis while its physiological function in the development of mammalian brain remains unclear. In this study, we focused on the role of *Alk* in the cerebral cortical development in mice. We employed RNAi and pharmacological inhibition in cultured human neural progenitor cells (hNPCs) derived from embryonic stem cells and C57/B6 wild-type embryonic mice to inhibit Alk signaling, respectively. We examined the effects of Alk inhibition on neuronal proliferation, apoptosis and cell cycle in cultured hNPCs by FACS and immunocytochemistry. In addition, we analyzed the neuronal proliferation, differentiation and migration in embryonic mouse brain by immunohistochemistry after Alk signaling disruption. The results indicate that Alk regulates cortical development by promoting the proliferation and survival of neural progenitor cells.

Disclosures: R. Mao: None. **G. Wang:** None. **R. Deng:** None. **Z. Jia:** None. **Z. Zhou:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.11/B1

Topic: A.01. Neurogenesis and Gliogenesis

Support: March of Dimes Foundation Basil O'Connor Starter Scholar Research Award 5-FY13-194 RWS

NIH R01NS085023 to RWS

NIH R01GM112744 to RWS

Title: Novel genetic modifier of forebrain size in a ciliary mutant of Ttc21b

Authors: *J. SNEDEKER, W. GIBBONS, D. PROWS, R. W. STOTTMANN
Cincinnati Childrens Hosp. Med. Ctr., Cincinnati, OH

Abstract: The primary cilium, a microtubule based extension of the cell membrane, is a critical signaling center for proper brain development and function. Patients with ciliopathies frequently suffer from cognitive impairment. In a ciliopathy patient cohort, heterozygosity for the gene *TTC21B* was found to be the most common mutation. We have previously demonstrated that mice lacking *Ttc21b* have impaired retrograde trafficking in the cilium and a reduction in forebrain size (microcephaly). Interestingly, the severity of the microcephaly in homozygous *Ttc21b* null mutants is considerably affected by the genetic background. *Ttc21b* mutants on an FVB/NJ (FVB) background develop a forebrain significantly smaller than mutants on a C57BL/6J (B6) background. In order to identify potential genetic modifiers of microcephaly in *Ttc21b* mutants and more generally inform neural development, a Quantitative Trait Locus (QTL) analysis was performed. B6 and FVB animals carrying the *Ttc21b* mutation were crossed to produce F1 animals. These were used in an analysis of 96 F2 *Ttc21b* mutants. A QTL analysis of forebrain size was performed with r/QTL and a significant correlation between forebrain size and genetic background was discovered on distal chromosome 4. Analysis of this region of interest (ROI) confirmed that F2 mutants homozygous for FVB on distal chromosome 4 had significantly smaller forebrains than mutants homozygous for B6. A congenic backcross was performed, designed to produce pure FVB mice everywhere across the genome except for the ROI, which would remain B6. After 5 generations of backcrossing, those mutants with B6 homozygosity in the ROI exhibited larger forebrains than those with homozygous FVB ROI. Analysis of the ROI produced an intriguing candidate gene, a brain specific orphan G-protein coupled receptor (GPCR), *Gpr63*. We have shown that *Gpr63* localizes to the cilium. Additionally there is a SNP between FVB and B6 which causes a missense mutation predicted to be deleterious in the FVB protein. Using CRISPR technology we have taken FVB mice and substituted the B6 variant SNP in *Gpr63*, and subsequently crossed in the *Ttc21b* allele. This strategy will allow us to validate the SNP, the gene, and the ROI as genetic modifiers of forebrain size in *Aln* mutants. Proper trafficking of GPCRs through the cilium has been shown to be critical for the proper regulation of Sonic Hedgehog signaling, which is known to be perturbed in *Ttc21b* mutants. *Gpr63* as a brain specific ciliary signaling modulator trafficked by *Ttc21b* is an intriguing model which supports two hypotheses of our lab: unique, tissue-specific roles of cilia and *Ttc21b* as a trafficking node in a network of ciliary proteins.

Disclosures: **J. Snedeker:** None. **W. Gibbons:** None. **D. Prows:** None. **R.W. Stottmann:** None.

Poster

114. Neural Progenitor and Stem Cell Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH-NIGMS Grant R21-GM114854

NSF Grant DBI-1455474

GWU Columbian College Facilitating Fund

Title: Mass spectroscopy proteomics of neural fated cell in the Xenopus embryo

Authors: C. LOMBARD-BANEK, 20037[1], *S. A. MOODY[2], P. NEMES[1]
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Abstract: Characterization of functionally important proteins is key to understanding normal and impaired development. However, recent studies found that the single-cell transcriptome may not be an accurate indicator of the proteome. While mass spectrometry (MS) is the technology of choice for the unbiased interrogation of the proteome, typical proteomics studies average across a large number of cells, thus limiting the interpretation of cell-to-cell heterogeneity. Here, we discuss a single-cell bottom-up proteomics approach that we developed using discovery (untargeted) MS to enable the quantitative analysis of protein changes as cells differentiate to neural fates. We chose the South African clawed frog (*Xenopus laevis*) embryo, in which cells follow stereotypical tissue fate maps. To understand how proteins change at the single-cell level during development of neural tissues, we developed an *in-situ* microprobe single-cell MS. This sampling technique enabled us to reproducibly collect an ~10% fraction of the single-cell content as cells gave rise to neural tissue fated cell clones through progressive stages of the embryo development. Extracted proteins were sequenced and quantified using a custom-built capillary electrophoresis (CE) electrospray ionization (ESI) mass spectrometer. This strategy enabled, for the first time, the discovery quantification of protein production in the neural fated cell clones across four developmental stages, including the cleavage (16- and 32-cell embryo) and blastula (64- and 128-cell embryo) stages. These measurements allowed us to identify 470 proteins and quantify ~450 across the cell lineages. Cluster analysis on the quantitative data uncovered diverse spatial and temporal expression across cell lineages, providing exciting new data for functional studies. Furthermore, our technology is also applicable to smaller cells and other models, which we demonstrate for the 2-cell zebrafish embryo. Microprobe single-cell MS opens

new prospects to understand mechanisms underlying neural tissue formation in powerful vertebrate developmental models.

Disclosures: C. Lombard-Banek: None. **S.A. Moody:** None. **P. Nemes:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.13/B3

Topic: A.01. Neurogenesis and Gliogenesis

Title: Interactions between β1-integrin and bone morphogenetic protein signaling in neural stem cells

Authors: *J. CHEN[1], C.-Y. PENG[2], J. A. KESSLER[2]
[2]Davee Dept Neurol, [1]Northwestern Univ., Chicago, IL

Abstract: Bone morphogenetic protein (BMP) and β1-integrin signaling are important pathways that regulate neural stem and progenitor cell (NSC) maintenance and differentiation. Previous work from our laboratory has shown that BMP signaling in postnatal and adult NSCs promotes exit from cell cycle and increases astrocyte differentiation. By contrast, β1-integrin signaling promotes maintenance of NSC stemness, and knockout of β1-integrin increases astrocyte differentiation. These findings suggest that β1-integrin and BMP signaling converge on, and have opposing effects on, astrocyte differentiation.
It is known that β1-integrin interacts with type 1 BMP receptors, but the exact nature of the BMP and β1-integrin signaling interaction is unclear. One common downstream effector of BMP and β1-integrin signaling is the transcription factor yes-associated protein (YAP1), a component of the Hippo pathway. Previous studies have implicated BMP as a regulator of YAP1 expression and subcellular localization in many different cells and processes, including heterotopic ossification as well as numerous cancer types. We find that BMP and β1-integrin signaling have opposing effects on total levels of YAP1 protein phosphorylation and subcellular localization in cultured NSCs. We hypothesize that the effects of BMP and β1-integrin on NSC cell cycle kinetics and cell fate determination converge at the level of YAP1 regulation. To investigate this, we have generated transgenic mice that carry loxP sites flanking both the BMP type 2 receptor subunit and the β1-integrin loci under the control of a tamoxifen-inducible Nestin-Cre transgene. We will present findings that address the mechanisms by which BMP and β1-integrin signaling converge on YAP1-mediated transcriptional regulation and astrocyte differentiation in NSCs.

Disclosures: J. Chen: None. **C. Peng:** None. **J.A. Kessler:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.14/B4

Topic: A.01. Neurogenesis and Gliogenesis

Support: Marga und Walter Boll-Stiftung 210-12-12

Marga und Walter Boll-Stiftung 210-10-15

Title: Characterization of primary neural stem cells on elastic substrates *In vitro* as a model of the physiological cerebral milieu

Authors: *M. A. RUEGER[1], S. BLASCHKE[1], S. U. VAY[1], J.-A. ABRAHAM[2], C. LINNARTZ[2], G. DREISSEN[2], M. HOFFMANN[2], N. HERSCH[2], R. MERKEL[2], G. R. FINK[1], B. HOFFMANN[2]
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Abstract: In the brain, neural stem cells (NSC) are tightly regulated by external signals and biophysical cues through the local microenvironment or “niche”. Besides the well-characterized effects of cytokines, chemokines or cell-cell contact on stem cell function, the influence of the environmental mechanical properties on NSC are incompletely understood. In particular, tissue elasticity is known to fundamentally affect the function of various cell types in the body. Notably, the brain is among the softest tissues in the human body, with an elasticity of <1 kPa. Thus, standard cell culture conditions on glass plates with an elasticity of 7 GPa constitute an unphysiological microenvironment. We here aimed to characterize the effects of elastic substrates on crucial functions of NSC.
Primary rat neural stem cells were grown on polydimethylsiloxane- (PDMS-) based gels to simulate the physiological microenvironment of the live brain. PDMS-coated cell culture plates were generated in various degrees of elasticity, ranging from 1-50 kPa; regular glass plates served as control condition. Survival, proliferation, differentiation speed and differentiation fate of NSC were characterized in order to assess key stem cell functions.
Survival of NSC on the PDMS-based substrates was not impaired. The proliferation rate negatively correlated with substrate elasticity, cautiously suggesting that the physiological microenvironment might support quiescence of stem cells. Upon mitogen withdrawal, NSC differentiation was accelerated on substrates with high elasticity, with a trend towards neuronal differentiation.
Data suggest that primary NSC are relevantly affected by the mechanical properties of their microenvironment. Further characterization of the effects of elasticity on NSC will advance our understanding of key mechanisms in development and disease.

Disclosures: **M.A. Rueger:** None. **S. Blaschke:** None. **S.U. Vay:** None. **J. Abraham:** None. **C. Linnartz:** None. **G. Dreissen:** None. **M. Hoffmann:** None. **N. Hersch:** None. **R. Merkel:** None. **G.R. Fink:** None. **B. Hoffmann:** None.

Poster

114. Neural Progenitor and Stem Cell Development

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Topic: A.01. Neurogenesis and Gliogenesis

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NIH T32 NS082174

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National Multiple Sclerosis Society

Title: The N-glycan branching pathway alters neural stem cell biophysical properties and shifts fate potential towards astrogenesis

Authors: *A. R. YALE[1], J. L. NOURSE[1], K. R. LEE[1], S. N. AHMED[2], J. ARULMOLI[1], L. P. MCDONNELL[1], G. A. BOTTEN[3], E. S. MONUKI[1], M. DEMETRIOU[1], L. A. FLANAGAN[1]
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Abstract: Neural stem cells have the potential to treat many neurological diseases and injuries due to their ability to secrete beneficial factors and to form the major cell types that comprise the central nervous system. However, these cells generate a heterogeneous population of neural stem and progenitor cells (NSPCs) when expanded *in vitro*, which can confound transplant outcomes. A better understanding of the cellular characteristics defining or regulating distinct progenitors in the lineage is important for predicting or controlling the types of cells formed from a population of NSPCs. We found previously the electrophysiological property membrane capacitance distinguishes neurogenic and astrogenic progenitors and hypothesized that cell surface glycosylation may affect membrane capacitance. Glycosylation modifies the structure, retention, and function of almost all proteins on the cell surface, thus influencing their interactions with extracellular cues. A gene array identifying glycosylation enzyme expression levels in E12 (neurogenic) and E16 (astrogenic) mouse NSPCs revealed differences between the two in N-

glycan branching enzymes. Further analysis showed higher activity in the branching pathway in E16 NSPCs compared to E12 NSPCs *in vitro* and *in vivo*. Enriched astrogenic progenitors expressed higher levels of N-glycan branching enzymes than did unsorted controls. Supplementing E12 NSPCs with N-acetylglucosamine (GlcNAc) to drive the branching pathway increased both highly-branched N-glycans on the cell surface and membrane capacitance. GlcNAc treatment amplified astrocyte generation at the expense of both neuron and oligodendrocyte formation, showing that altering highly-branched N-glycans affects fate choice. GlcNAc can be utilized in multiple metabolic processes, so N-glycan branching was blocked with kifunensine to test whether GlcNAc's effects on fate are dependent on this pathway. Kifunensine and GlcNAc co-treated cells did not form highly-branched N-glycans and did not exhibit the same effects on fate as GlcNAc treated cells. These data show that the effect of GlcNAc on cell fate is mediated by the formation of highly-branched N-glycans and identify the N-glycan branching pathway as a significant regulator of membrane capacitance and fate choice in the neural lineage.

Disclosures: **A.R. Yale:** None. **J.L. Nourse:** None. **K.R. Lee:** None. **S.N. Ahmed:** None. **J. Arulmoli:** None. **L.P. McDonnell:** None. **G.A. Botten:** None. **E.S. Monuki:** None. **M. Demetriou:** None. **L.A. Flanagan:** None.

Poster

114. Neural Progenitor and Stem Cell Development

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 114.16/B6

Topic: A.01. Neurogenesis and Gliogenesis

Title: Development of an advanced media system for improved neuronal viability and function

Authors: *N. KAUR, J. SAGAL, B. LIU, M. DERR, Y. YAN, R. JOSEPHSON, D. KUNINGER
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Abstract: Neuronal cell cultures offer an indispensable tool for investigating fundamental questions in neurobiology and applied applications in cell therapy and drug discovery. As such, the ability to establish and maintain primary neuronal cultures is essential for the comprehensive study of neuronal development and function. Neurons are usually cultured in serum-free systems which include a basal medium and supplements such as Neurobasal™ medium supplemented with B-27™ respectively. Here, we describe a new serum free neuronal media system that provides significant improvements for long term viability and functionality of primary and PSC-derived neurons *in vitro*. This new system, comprising a neuronal basal medium (Neurobasal ™ Plus) and serum-free supplement (B-27™ Plus), is specifically optimized for the maturation and viability of primary rat, mouse and human PSC-derived neurons for long term cultures at both

low and high cell density. Performance was evaluated by a number of criteria including neurite outgrowth, viability, relative purity and functionality. Typically cultures were assessed at 7, 14 and 21 days following plating primary neurons or addition of maturation medium to iPSC-derived neurons. The cultures were assessed for cell survival and neurite outgrowth by quantitative morphometric analysis using the Incucyte® Zoom live cell imaging system. Neuronal cell numbers (viability over time) was assessed by quantitative immunocytochemistry (ICC) using HuC/HuD to demarcate neuronal populations. HuC/HuD staining is localized to the cell body of neurons, facilitating quantification and throughput using an automated high content analysis system. In addition, primary rat neurons cultured in Neurobasal ™ Plus and B-27™ Plus system showed higher maturity showing superior levels of expression of synaptic markers Synapsin and MAP2 by ICC and produced higher spike rates on multielectrode arrays (MEA). Taken together these results demonstrate that our new B-27™ Plus Supplement and Neurobasal™ Plus Medium culture system is a superior solution to the current trusted standards used for culturing primary neurons, and maturing and maintaining hPSC-derived neurons.

Disclosures: **N. Kaur:** None. **J. Sagal:** None. **B. Liu:** None. **M. Derr:** None. **Y. Yan:** None. **R. Josephson:** None. **D. Kuninger:** None.

Poster

114. Neural Progenitor and Stem Cell Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant HD072035

Rita Allen Foundation

Whitehall Foundation

Title: Regulation of neural progenitor competence through genome architecture reorganization

Authors: *M. KOHWI[1], T. HAFER[2], N. MOLOTKOVA[2]
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Abstract: The development of a complex brain requires the generation of diverse neural cell types at the right time, place, and relative abundance. Neural progenitors produce this diversity in part by sequentially specifying different cell types in a stereotyped order. Over time, they lose potential (“competence”) to make the earlier-born cell types while acquiring the competence to produce the later-born fates. How does this occur, and how does it impact brain development? We use the Drosophila embryo as a model to study the mechanisms that underlie competence regulation.

The fly ventral nerve cord harbors ~30 distinct neuroblasts (fly neural progenitors), each of which gives rise to a unique lineage of neurons and glia in an invariant birth order. These neuroblasts can be individually identified and tracked over developmental time, making this an ideal system to study the effects of gene manipulation on lineage progression and competence transitions in vivo. As each neuroblast divides, it sequentially expresses a series of transcription factors, Hunchback (Hb) - Kruppel - Pdm - Castor with each division; Hb, the first of the series, specifies early-born neural fate. Neuroblast competence to specify early-born neurons is limited. We discovered that this restriction is due to a relocation of the *hb* genomic locus from the neuroblast nuclear interior to the periphery, where it becomes permanently silenced. This relocation occurs in a gene, cell type, and developmental stage specific manner, underscoring the dynamism and high level of regulation of the neuroblast genome architecture. Our recent preliminary data comparing neuroblasts at different developmental stages suggest a genome-wide restructuring of chromatin architecture over time. We are using a series of genetic, biochemical, and molecular approaches to examine the global changes in neuroblast genome architecture, how intrinsic and extrinsic cues control the timing of such changes, and the biological consequences of this reorganization on neural diversity.

Disclosures: **M. Kohwi:** None. **T. Hafer:** None. **N. Molotkova:** None.

Poster

114. Neural Progenitor and Stem Cell Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R00ES022992

Title: Acute effects of thyroid hormone on the developing tadpole telencephalon

Authors: *J. P. KITCHEN[1], C. K. THOMPSON[2]
[1]Translational Biology, Medicine, and Hlth., Virginia Tech., Blacksburg, VA; [2]Sch. of Neurosci., Viriginia Tech., Blacksburg, VA

Abstract: Thyroid hormone (TH) plays an important role in the developing brain, but the specific effects of TH on early brain development are less well characterized. This is particularly true about the telencephalon, an intricate neural circuit that regulates a variety of complex behaviors. *Xenopus laevis t*adpoles are a useful model for examining the effects of TH on brain development because TH induces rapid and gross changes in the brain during metamorphosis, and their external development allows for direct observation of the brain in vivo that would be difficult to undertake in mammalian models. Here we show that six days of exogenous TH treatment induces robust change in the tadpole telencephalon. We found that while cell

proliferation in the telencephalon was increased in response to exogenous TH, the overall volume did not change, despite many changes in underlying telencephalon morphology. This lack of telencephalon volume increase may have been offset by a significant increase in apoptosis in response to TH treatment. In addition, several TH-sensitive genes substantially differed in their expression between the telencephalon and the rest of the brain. Ongoing experiments will evaluate changes in neuronal morphology in the telencephalon using time-lapse *in vivo* imaging. Our results indicate that TH affects cellular and molecular events in the developing telencephalon in ways that substantially differ when compared to other parts of the brain.

Disclosures: J.P. Kitchen: None. **C.K. Thompson:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

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Program#/Poster#: 115.01/B9

Topic: A.02. Postnatal Neurogenesis

Support: Science Foundation Ireland Grant SFI/IA/1537

Title: Deletion of Tlx and social isolation impairs exercise-induced neurogenesis in the adolescent hippocampus

Authors: *Y. M. NOLAN, D. A. KOZAREVA, O. F. O'LEARY, J. F. CRYAN
Univ. Col. Cork, Cork, Ireland

Abstract: Adolescence is a sensitive period of neurodevelopment during which life experiences and the surrounding environment can have profound effects on the brain. Neurogenesis is a neurodevelopmental process of generating functional neurons from neural stem cells which occurs throughout the lifespan in the hippocampus. Adult hippocampal neurogenesis has been shown to play a role in learning and memory and in mood regulation. It has also been shown to be influenced by environmental factors such as exercise and stress in the adult. Intrinsic factors that regulate hippocampal neurogenesis include the orphan nuclear receptor TLX (Nr2e1) which is primarily expressed in neurogenic niches of brain. While mechanisms regulating adult neurogenesis have been widely studied, less is known however on how neurogenesis is affected during the adolescent period. The aim of this study was to investigate the influence of social isolation stress on exercise-induced increase in neurogenesis during adolescence and to determine a role for its intrinsic regulation by TLX. Single or pair-housed wild-type mice were housed in sedentary conditions or allowed free access to running wheels for 3 weeks during the adolescent period. We demonstrate that social isolation of mice during adolescence does not impact upon hippocampal neurogenesis, as determined by immunohistochemical analysis of the

survival of newborn neurons. However, social isolation prevents an exercise-induced increase in hippocampal neurogenesis in these mice. Furthermore, we show that there is no increase in neurogenesis in Nr2e1$^{-/-}$ mice with access to running wheels, which suggests that TLX is necessary for the pro-neurogenic effects of exercise.

Disclosures: **Y.M. Nolan:** None. **D.A. Kozareva:** None. **O.F. O'Leary:** None. **J.F. Cryan:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.02/B10

Topic: A.02. Postnatal Neurogenesis

Support: SFI/IA/1537

Title: Differential effects of exercise during adolescence and adulthood on cognition and plasticity

Authors: *J. D. O'LEARY[1], A. E. HOBAN[1], C. BROUWERS[1], A. M. SULLIVAN[1], O. F. O'LEARY[1,2], J. F. CRYAN[1,2], Y. M. NOLAN[1,2]
[1]Anat. and Neurosci., Univ. Col. Cork, Cork, Ireland; [2]APC Microbiome Inst., Cork, Ireland

Abstract: Adolescence is a critical period for postnatal brain maturation and thus a time for increased susceptibility to developing emotional and cognitive-related disorders. Exercise during adulthood has been shown to increase hippocampal neurogenesis and enhance cognition. However, the impact of exercise during adolescence on the brain and behaviour in adulthood remains to be fully elucidated. The aim of this study was to determine the impact of exercise during adolescence on neural plasticity and cognitive performance in hippocampal neurogenesis-dependant and independent tasks.
Adolescent (4 week) and adult (8 week) male Sprague Dawley rats were divided into sedentary control (n = 40) and exercise (n = 40) groups. All rats were pair housed in either standard housing or with continuous access to a running wheel. Following four weeks of exercise, rats (8 weeks or 12 weeks) performed a location discrimination and reversal learning task in a touchscreen operant chamber (n = 40) or non-touchscreen hippocampal-dependent behavioural tasks; spontaneous alternation in the y-maze, contextual fear conditioning and novel object recognition (n = 40). Tissue was collected for analysis of neural plasticity (PSD-95, synaptophysin, BDNF, TLX and DCX) (n = 40).
The results indicate that exercise during adolescence and adulthood enhanced reversal learning in the location discrimination task ($p<0.05$). Interestingly, acquisition of the location discrimination was unaffected by exercise. In addition, adolescent exercise impaired contextual fear recall

($p<0.05$), while exercise during adulthood enhanced contextual fear recall ($p<0.05$). Similarly, spontaneous alternation was impaired following adolescent exercise ($p<0.05$), but was unaffected by adult exercise while novel object recognition was unaffected by adolescent and adulthood exercise. Adolescent exercise also increased mRNA expression of PSD-95, synaptophysin, BDNF, TLX and DCX in the hippocampus. Analysis of hippocampal mRNA expression of plasticity markers following exercise in adulthood is ongoing.
Growing evidence suggests that adolescence is a critical period for brain maturation and that experience during this time shapes behaviour and cognitive processes in later life. These findings suggest that exercise enhanced prefrontal cortex-dependent reversal learning regardless of when exercise occurred, but had a differential effect on hippocampal associated behaviours. Investigations into the impact of exercise during adulthood on neural plasticity are ongoing.

Disclosures: J.D. O'Leary: None. **A.E. Hoban:** None. **C. Brouwers:** None. **A.M. Sullivan:** None. **O.F. O'Leary:** None. **J.F. Cryan:** None. **Y.M. Nolan:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: SFI Grant 12/IA/1537

Title: The orphan nuclear receptor TLX regulates hippocampal transcriptome changes induced by IL-1β

Authors: *C. S. O'LEIME[1], A. E. HOBAN[1], D. A. KOZAREVA[1], C. M. HUESTON[1], R. M. STILLING[2], J. F. CRYAN[1,2], Y. M. NOLAN[1,2]
[1]Anat. and Neurosci., Univ. Col. Cork, Cork, Ireland; [2]Alimentary Pharmabiotic Ctr., Cork, Ireland

Abstract: TLX is an orphan nuclear receptor involved in the regulation of hippocampal neurogenesis by promoting neural progenitor cell (NPC) proliferation, while inflammation has been shown to have negative effects on hippocampal neurogenesis. Specifically, the pro-inflammatory cytokine IL-1β has been shown to suppress NPC proliferation as well as TLX expression. However, it is unknown whether TLX itself is involved in regulating the inflammatory response in the hippocampus. To explore the role of TLX in IL-1β-mediated inflammation, we assessed changes in the transcriptional landscape of the hippocampus of TLX knockout (KO) mice compared to wildtype (WT) littermate controls with and without intrahippocampal injection of IL-1β using a whole transcriptome RNA sequencing approach. We demonstrated that in TLX KO mice compared to WT controls there is an increase in the

transcription of genes involved in the promotion of inflammation and regulation of cell chemotaxis (e.g. CXCR1, CXCR2, TLR4) and a decrease in the expression of genes relating to synaptic signalling (e.g. LYPD1, SYT4, CPLX2). Furthermore, we demonstrate that mice lacking in TLX share a similar increase in 176 genes involved in regulating inflammation (e.g. CXCL1, TNF, IL-1B) as WT mice injected with IL-1β into the hippocampus. KO mice injected with IL-1β display a unique transcriptional profile unlike WT after IL-1β exposure. This is likely due to the KO mice already having an exaggerated inflammatory profile and are thus primed to respond differently to an inflammatory stimulus such as IL-1β. Thus, we demonstrate that TLX is necessary for development of an inflammatory response to cytokine stimulation.

Disclosures: C.S. O'Leime: None. **A.E. Hoban:** None. **D.A. Kozareva:** None. **C.M. Hueston:** None. **R.M. Stilling:** None. **J.F. Cryan:** None. **Y.M. Nolan:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: NNX07AP84G

K02DA023555

Title: Exposure to space radiation reduces neurogenesis but enhances pattern separation in both aversive and appetitive testing platforms in mature mice

Authors: R. P. REYNOLDS[1], C. W. WHOOLERY[2], M. J. LUCERO[2], N. ITO[2], R. L. REDFIELD[2], D. R. RICHARDSON[2], G. PALCHIK[2], S. MUKHERJEE[2], P. D. RIVERA[2], S. G. BIRNBAUM[2], B. P. C. CHEN[2], S. YUN[3], *A. J. EISCH[1,3,2]
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Abstract: Astronauts traveling to Mars will be exposed to space radiation made up of high-atomic number and -energy (HZE) particles, such as 56Fe. This unavoidable radiation has been shown to decrease hippocampal function (e.g. learning and memory) in mice and rats. While this raises concern that space radiation will compromise astronaut health and mission success, most data are from young adult rodents (2 month-old at irradiation [IRR]) which are age-equivalent to teenage humans. Thus, it is unknown how the fully mature brain responds to HZE radiation, and how this radiation affects behavioral performance, particularly on more challenging learning tasks such as hippocampal-dependent pattern separation. To determine how space radiation

influences such behavior in “astronaut age”-equivalent mice (6-month at IRR), young adult or mature male mice received whole-body radiation at the Brookhaven National Laboratories synchrotron (56Fe, 0 cGy, Fractionated or Non-Fractionated 20 cGy, 600 MeV/n) and hippocampal-dependent behavior was evaluated beginning one month post-IRR. Extending prior work performed with contextual fear conditioning, mice irradiated during young adulthood displayed dose- and HZE particle-dependent decrements in context-dependent fear conditioning, a shock-based pattern separation test. In contrast, mature irradiated mice performed surprisingly better in both the aversive context-dependent fear conditioning as well as an appetitive touchscreen pattern separation tasks. For example, IRR mice were able to separate distinct contexts or images faster and more consistently, while there was no difference in rule-based, reversal, or location learning. Thus, mice irradiated in maturity can pattern separate better than controls on both appetitive and aversive testing platforms. Mechanistic studies are underway to explain this radiation-induced improvement in pattern separation for male mice, including assessment of hippocampal neurogenesis and interneuron number and function.

Disclosures: **R.P. Reynolds:** None. **C.W. Whoolery:** None. **M.J. Lucero:** None. **N. Ito:** None. **R.L. Redfield:** None. **D.R. Richardson:** None. **G. Palchik:** None. **S. Mukherjee:** None. **P.D. Rivera:** None. **S.G. Birnbaum:** None. **B.P.C. Chen:** None. **S. Yun:** None. **A.J. Eisch:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: ZIAMH002784

Title: Investigating the role of adult hippocampal neurogenesis on cognitive affective bias

Authors: R.-M. KARLSSON, A. S. WANG, *H. A. CAMERON
NIMH, NIH, Bethesda, MD

Abstract: Patients with depression frequently ruminate over their perceived failures and criticism and have an exaggerated response to negative feedback during laboratory testing. Similar biases have been shown in animals, providing an opportunity to investigate the underlying processes of this behavior. Our laboratory has developed a genetic model in which we can completely inhibit adult neurogenesis by giving an antiviral drug to transgenic rats that express herpes simplex virus thymidine kinase (TK) in neural stem cells. We have previously shown that mice lacking neurogenesis exhibit an anxiodepressive-like phenotype as well as decreased hippocampal network activation and reduced defensive behavior following ambiguous

threat cues. We sought to extend these findings by asking whether rats lacking adult hippocampal neurogenesis show different behavior than wild-type (WT) controls in tests of cognitive affective bias. Using a spatial cognitive task, responses to ambiguous spatial cues indicated that rats lacking adult hippocampal neurogenesis were 'pessimistic' compared to WT controls. In an operant judgement bias task using auditory stimuli associated with a food reward or a foot shock and a novel ambiguous stimulus, which typically shows high proportions of pessimistic rats, both WT and TK rats showed 'pessimistic' behavioral responses. However, when the auditory stimuli where associated with either large or small rewards, ambiguous tones were interpreted 'optimistically' by both genotypes. This indicates that animals lacking adult hippocampal neurogenesis are able to respond normally to ambiguous stimuli when the task produces a strong bias. Future studies are needed to understand the role of adult hippocampal neurogenesis on cognitive affective bias.

Disclosures: R. Karlsson: None. **A.S. Wang:** None. **H.A. Cameron:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: NIH grant NS080913

Title: Origins of age-related neurogenesis decline

Authors: *M. A. BONAGUIDI[1], A. IBRAYEVA[1], E. PU[1], D. JORG[2], G.-L. MING[3], H. SONG[4], B. SIMONS[2]
[1]Stem Cell Biol. & Regenerative Med., USC, Los Angeles, CA; [2]Cavendish Lab., Cambridge Univ., Cambridge, United Kingdom; [3]Dept Neurol & Neurosci, Johns Hopkins University, Inst. for Cell Engin, Baltimore, MD; [4]Johns Hopkins Univ. SOM, Baltimore, MD

Abstract: Equilibrium between self-renewal and cell differentiation is preserved by endogenous stem cells in most tissues through late life. However, neurogenesis in the adult rodent hippocampus diminishes significantly by middle age of unclear origins. By using *in vivo* single cell linage tracing and computational reconstruction, we identify two radial glia-like (RGL) neural stem cell (NSC) populations. These cells differentially contribute to cell production under physiological and injury conditions in the young adult. During aging, these cohorts serve as short-term and 'long-term' NSCs. Long-term RGL behaviors change in attempt to restore homeostasis during aging. Yet, loss of NSC homeostasis is ultimately driven by increased RGL quiescence and slowing expansion rate. Our study elucidates cellular origins of neurogenesis decline and may serve as a new mammalian stem cell model to study early-onset cellular aging.

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Poster

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Topic: A.02. Postnatal Neurogenesis

Support: NIMH R21 107945

NIH K02 DA 023555

Title: Targeting entorhinal cortex-hippocampus circuitry as a therapeutic strategy for depression

Authors: *S. YUN[1,2], R. REYNOLDS[2], G. ZANNI[2], A. SEGEV[3], S. MUKHERJEE[3], D. RICHARDSON[3], M. DESALLE[2], S. KOURRICH[3], A. EISCH[1,2,3]
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Abstract: Humans with and rodent models of Major Depressive Disorder are marked by dysregulated hippocampal circuitry, and antidepressant treatments like electroconvulsive shock ameliorate these hippocampal changes. From such work, a promising framework for discovery of new antidepressants has emerged: find treatments that “recalibrate” depression-linked dysfunctional neural circuits and behavior. Indeed, other approaches to “stimulate” neural circuits - such as deep brain stimulation (DBS) - have been successful in reversing depression-related symptoms and neuropathology, particularly in the hippocampus. Strikingly, in the context of depression, DBS has only been targeted to non-hippocampal brain regions, such as the nucleus accumbens and subcallosal cingulate. While direct stimulation of the hippocampus has generally negative effects, we have recently discovered that stimulation of a key hippocampal input, the entorhinal cortex [Ent]-DG circuitry, is antidepressive. As the Ent-DG projection contains both glutamatergic as well as GABAergic projection neurons, here we explored whether cell-type specific stimulation of Ent efferents underlies antidepressive-like effect. To this end, we used chemogenetics and Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology to control the excitability of either efferent glutamatergic neurons (via AAV-DIO-hM3Dq Ent infusion into CamKIIa-icre transgenic mice) or efferent GABAergic neurons (via AAV-DIO-hM3Dq Ent infusion into Somatostatin (SST)- and Parvalbumin (PV)-cre transgenic mice). Chronic, but not acute, stimulation of Ent-DG glutamatergic neurons is antidepressive and increases hippocampal neurogenesis, an activity-dependent process. Interestingly, our pilot data suggest stimulation of Ent SST interneurons and PV interneurons induces depressive-like behavior after chronic stress. However, this is likely influenced by the large proportion of long-

range projecting SST and PV interneurons that innervate CA1 and CA3. We are currently examining the terminal specificity of Ent glutamatergic and Ent SST or PV GABAergic neurons (i.e. CA1/CA3 vs. DG) to further understand how Ent cell-type specific stimulation drives antidepressive behavior or depressive like behavior. Our study will dissect how highly promising targets for the treatment of depression - Ent-hippocampal circuitry and DG neurogenesis - work together to regulate affective behaviors.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: BMBF (01GI9905, 01GZ070)

IZKF Jena

Title: Cyclin D2 is required for the establishment of the adult neural stem cell pool during postnatal development of the dentate gyrus

Authors: *A. URBACH[1], V. KNÖLKER[1], O. PASTOR[2], S. MARTIN[2], F. TETZLAFF[1], R. N. BADELT[1], J. M. ENCINAS[2], O. W. WITTE[1]
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Abstract: The dentate gyrus (DG) holds a specialized stem cell niche at the border between the granule cell layer and the hilus - the subgranular zone (SGZ) - that produces new neurons throughout life. Morphogenesis of the DG is complex and continues from around mid-gestation to early postnatal periods, ultimately leading to the formation of the SGZ during the second postnatal week in mice. Our previous studies revealed that the production of new neurons in the adult SGZ critically depends on cyclin D2 (D2). Unlike Cyclin D1-positive cells, which are equally abundant in the SGZ, D2-positive cells are highly proliferative (D2: approx. 90% $MCM2^+$, D1: approx. 30% $MCM2^+$; age: P70). D2 was detected in all progenitor subtypes of the SGZ with preference for the earlier stages (type 2). Remarkably, D2 was the exclusive D-cyclin found in adult NSCs. We next examined the effects of a functional ablation of D2 (D2KO) on adult NSCs. We knew from our earlier studies that D2KO mice exhibit deficits in postnatal cell generation, culminating in nearly complete loss of cell birth at the age when granule cell production shifts to the SGZ (between P14 and P28). Now, by using D2KO/Nestin-GFP double-

transgenic mice, we observed that the DG of adult D2KO mice is virtually devoid of radial NSCs. The few remaining GFP-positive NSCs displayed a multipolar morphology and were often found in ectopic locations, but lacked the astrocyte marker S100b. Furthermore, none of these cells were actively proliferating ($Ki67^+$) as occasionally seen for radial NSCs in wildtype mice. Taken together, these results suggest that D2 expression is essential for the formation of the adult NSC pool during postnatal DG development. To further explore this hypothesis, we currently investigate the effects of D2KO on different progenitor cell populations at early postnatal ages. Our preliminary data indicate that early development of the DG tertiary matrix is unaffected by D2KO. However, the population of radial NSCs in the developing SGZ fails to expand from P7 to P14.

Disclosures: **A. Urbach:** None. **V. Knölker:** None. **O. Pastor:** None. **S. Martin:** None. **F. Tetzlaff:** None. **R.N. Badelt:** None. **J.M. Encinas:** None. **O.W. Witte:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.09/B17

Topic: A.02. Postnatal Neurogenesis

Support: ZIAMH002784

Title: Adult hippocampal neurogenesis impacts the expression of male aggression

Authors: *M. C. TSUDA, H. A. CAMERON
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Abstract: Adult neurogenesis affects many types of behavior, but few studies have examined its role in social interactions. The aim of the present study was to investigate the role of adult hippocampal neurogenesis in different forms of male aggression. We inhibited adult hippocampal neurogenesis for 8 weeks by giving valganciclovir in male transgenic mice expressing the herpes simplex virus thymidine kinase (TK) under a GFAP promoter. Both TK and wild-type (WT) littermate controls were single housed for one week and tested for either offensive or defensive aggression in the resident-intruder paradigm. To measure offensive aggression, WT and TK mice were tested in their home cage as the resident male for 3 consecutive days a week, for a total of 2 weeks, against a group-housed, unfamiliar intruder male. Aggression directed at the intruder male by the resident was analyzed for each test. During both weeks of testing, TK mice showed fewer aggressive bouts, shorter duration of aggression and longer latency to exhibit aggression towards the intruder compared to WT mice, suggesting reduced levels of offensive aggression in TK mice. To assess defensive aggression, a separate cohort of WT and TK male mice became the intruders in the resident-intruder test two times, 1

week apart. WT and TK mice were placed into the cage of an unfamiliar single-housed resident male and we measured WT and TK avoidance and attack behaviors during each resident attack. In both tests, resident males equally attacked both WT and TK mice. Both WT and TK mice exhibited a defensive behavior in response to the resident attacks, however, TK mice showed no defensive attack and only defensive avoidance behavior whereas WT mice showed both defensive attack and avoidance behaviors. These results suggest that adult hippocampal neurogenesis plays an important role in the expression of both offensive and defensive aggression in male mice.

Disclosures: **M.C. Tsuda:** None. **H.A. Cameron:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: R37HD059288

K02DA023555

NNX15AE09G

Title: Adult hippocampal neurogenesis following mild traumatic brain injury

Authors: ***K. L. CLARK**[1,2], S. YUN[1,2], H. E. METHENY[1], G. ZANNI[1], A. S. COHEN[1,2], A. J. EISCH[1,2,3]
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Abstract: Traumatic brain injury (TBI) affects over 1.5 million new people in the United States annually, ranging from mild injury - with only transient changes in mental state - to severe - leading to coma and even death. While many people make a substantial recovery, even those that experience mild TBI (mTBI) can suffer from long-lasting cognitive effects, particularly with neural processes underlying memory and attention. While the physiological changes underlying TBI-induced cognitive deficits are an area of intense study, the cellular and mechanistic underpinnings of these changes remain elusive. Contextual memory, a process that is reproducibly disrupted after mTBI, is critically dependent on adult hippocampal neurogenesis. Indeed, many groups have observed dynamic changes in hippocampal cell proliferation, neurogenesis, and neuronal survival following TBI. However, most of the published literature focuses on moderate and severe models of TBI. Because mTBI comprises such a large proportion of human brain injuries, it is critical to understand how mild injuries perturb the

hippocampal circuit and lead to long-lasting cognitive deficits. Therefore here we utilized an mTBI model and defined its influence on the dynamic process of adult hippocampal neurogenesis. Briefly, adult male C57BL/6J mice received mTBI via lateral fluid percussion injury (LFPI), and LFPI and sham surgery mice were examined for levels of neurogenesis via stereology at early (n=10) and late (n=10) time points following injury. All mice received a single injection of BrdU (150mg/kg i.p.) 3 days post injury to label proliferating cells. The short term group was killed 2 hours post BrdU, and brains sectioned, stained, assessed for indices of hippocampal neurogenesis, including proliferation (BrdU+ and Ki67+ cell number) and immature neurons (doublecortin [DCX]+ cell number). The long term group was killed 4 weeks post-BrdU and assessed for proliferation (Ki67+ cell number), immature neurons (DCX+cell number), and survival and fate of newly-born neurons (BrdU+ cell number and phenotyping). We predict that mTBI will induce a transient increase in proliferation and a longer-lasting increase in neurogenesis, resulting in mature neurons integrating into the dentate gyrus circuitry. These data will yield valuable insight about the maturation of newborn neurons and their integration into the hippocampal circuit after mTBI.

Disclosures: **K.L. Clark:** None. **S. Yun:** None. **H.E. Metheny:** None. **G. Zanni:** None. **A.S. Cohen:** None. **A.J. Eisch:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

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Topic: A.02. Postnatal Neurogenesis

Support: Pathway to Independence (PI) Award (4R00NS087096-03)

a NeuroBehavior Laboratory Pilot Project Research Award from the Harvard NeuroDiscovery Center

Title: The exercise hormone FNDC5 / irisin is required for the exercise-induced improvements of spatial learning and memory

Authors: *C. D. WRANN[1], M. F. YOUNG[1], M. P. JEDRYCHOWSKI[2], K. K. GERBER[2], B. J. CALDARONE[3], H. VAN PRAAG[4], B. M. SPIEGELMAN[2]
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Abstract: Exercise can induce adult hippocampal neurogenesis and improve cognitive function. However, the underlying molecular mechanisms remain largely unknown. We previously

identified FNDC5 and its secreted form irisin as being induced in by exercise and acting as a positive regulator of *Bdnf* expression and cell survival in culture. Now, we have generated global FNDC5 KO mice. The mice were born in Mendelian ration with no gross abnormalities. Motor function was unaltered in treadmill gait analysis or rotarod. Interestingly, significant differences in spontaneous activity, reduced exploration (open field, novel Y-maze, marble burying test), and possibly a mild cognitive impairment were observed in F5KO. F5KO mice have reduced adult hippocampal neurogenesis and reduced hippocampal *Bdnf* expression. Next, we tested whether exercise can improve the deficits in F5KO or if F5KO is required for the beneficial effects in running exercise. F5KO or wildtype controls were singly housed either with or without a running wheel for six weeks. Despite the same amount of running activity, the F5KO mice failed to show the typical exercise-induced improvements in spatial learning and memory in the Morris water maze. The effects on exercise-induced hippocampal neurogenesis and gene expression, such as *Bdnf*, are being evaluated. In summary, these data suggest that FNDC5 is not only important regulator in exercise but also required for normal hippocampal function. Future work will evaluate the therapeutic potential of FNDC5/irisin in neurological disorders.
This work was supported by a Pathway to Independence (PI) Award (4R00NS087096-03) and a NeuroBehavior Laboratory Pilot Project Research Award from the Harvard NeuroDiscovery Center (HNDC) to C.D.W.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: NSF Award No. 1553667

Title: Low-level silver nanoparticle exposure alters adult neural stem cell physiology

Authors: K. D. BROWN, K. J. NERHOOD, M. N. MENKING-HOGGATT, K. A. HUMPHREY, B. N. FORREN, R. J. COOPER, *N. SPITZER
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Abstract: Many consumer products and medical devices contain antimicrobial silver nanoparticles (AgNPs). These are generally considered safe because silver has been used for its antimicrobial properties for thousands of years. Manufactured AgNPs, however, are new and behave very differently in physiological environments than traditional ionic or colloidal silver. Due to their unique structure and high surface area, AgNPs easily cross biological barriers,

entering cells and tissues including the brain. Furthermore, AgNPs tend to bioaccumulate in tissues. Common consumer products shed low levels of AgNPs during normal use; these enter the body through ingestion or inhalation and travel to tissues via the bloodstream. Because of their tendency to bioaccumulate, this is of special concern in children, who may be exposed to low levels of AgNPs for extended times during critical neurodevelopmental periods. We used differentiating adult neural stem cells cultured from the rat subventricular zone as a model system to investigate the cellular and molecular action of AgNPs in neural cells. During differentiation *in vitro*, these cells mirror many of the processes involved in neurodevelopment and general neural function. Previously, we reported that low-level AgNP exposure led to formation of f-actin inclusions and disruption of cytoskeletal dynamics in these cells. Pharmacology in combination with immunocytochemistry and time-lapse microscopy showed that low-level AgNP treatment leads to relocalization of β-catenin within the cells, but that β-catenin signaling may not be directly involved in mediating AgNP-induced disruption of cytoskeletal dynamics and structure. To investigate *in vivo* effects, we orally administered AgNPs or vehicle control to Sprague-Dawley rats every day for a month. Brains were collected immediately after the month of exposure, or after an additional month of recovery. We found that silver entered the brain and that the levels of silver in the brain were not reduced after a month of recovery. We investigated astrocytes and microglia in brain sections using immunohistochemistry. AgNPs are increasingly prevalent in consumer products and this work will help determine if exposure through use of these products could have detrimental effects on the nervous system.

Disclosures: **K.D. Brown:** None. **K.J. Nerhood:** None. **M.N. Menking-Hoggatt:** None. **K.A. Humphrey:** None. **B.N. Forren:** None. **R.J. Cooper:** None. **N. Spitzer:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: AHA Grant 5101244

Whitehall Grant 5057606

Title: Mossy cell indirect pathway is required for adult neural stem cell maintenance and subsequent hippocampal neurogenesis

Authors: ***C.-Y. YEH**[1], B. ASRICAN[1], L. J. QUINTANILLA[2], X. MAO[4], T. HE[3], W. LU[4], J. SONG[1,2]

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Abstract: Mossy cells (MCs) represent a major population of excitatory neurons in the dentate gyrus of the adult hippocampus, a brain region where new neurons are continuously generated throughout life. Little is known about the influence of MCs on adult neural stem cells and hippocampal neurogenesis. Here we demonstrate that MCs functionally interact with radial neural stem cells (rNSCs) through both direct glutamatergic MC-rNSC pathway and indirect GABAergic MC-parvalbumin interneuron (PV)-rNSC pathway. Surprisingly, chemogenetic activation of MCs or optogenetic activation of MC projections promotes the quiescence of rNSCs, suggesting that indirect GABAergic pathway is sufficient to maintain rNSC quiescence. Interestingly, selective deletion of NR2B-containing NMDA receptors in PV interneurons leads to increased activation of rNSCs upon MC activation; while selective deletion of AMPA and NMDA receptors in rNSCs fails to significantly alter the quiescence of rNSCs. These data together provide causal evidence that MC indirect pathway mediated by NR2B receptors is required for maintaining rNSC quiescence. Strikingly, a small subset of MCs constituting approximately 25% of the total MC population are both necessary and sufficient in regulating rNSC quiescence, and chronic ablation of these MCs results in a significant reduction of rNSC pool and impaired hippocampal neurogenesis. Together, our study identifies MCs as a novel stem cell niche component that uses NR2B receptor dependent MC-PV pathway to control rNSC quiescence and activation which in turn impact rNSC maintenance and subsequent hippocampal neurogenesis.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: PSC-CUNY Award #69648-00 47

Title: Increased dopamine reduces hippocampal and striatal neurogenesis in a DAT knockdown mouse model

Authors: *C. O'BRIEN, A. TOROSSIAN, A. PEREZ, S. WODINSKY, K. NEWMAN, J. BEELER, C. PYTTE
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Abstract: Postnatal neurogenesis occurs primarily in two areas of the mammalian brain, the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and the subventricular zone (SVZ) of the lateral ventricles. New cells formed in SGZ migrate into the granular cell layer (GCL) of the dentate gyrus and cells formed in the SVZ migrate to the olfactory bulb and striatum. These neurogenic regions receive dopaminergic input from the mesolimbic pathway or nigrostriatal pathway, respectively. DA agonists can result in either an increase or decrease of neurogenesis perhaps in a receptor-specific manner.
Here we tested the role of dopamine (DA) in modulating the survival of new neurons using a mouse model with reduced expression of the dopamine transporter (DAT) to 10% that of wild-type levels (DAT-knockdown), thereby increasing dopamine in the synapse. We labeled dividing cells using bromodeoxyuridine (BrdU, 50 mg/kg in TBS) injected i.p. 2x/day for 4 days, in male and female DAT-knockdown (DATkd) mice along with wild-type (WT) controls. Thirty days after the last injection, the mice were perfused and brains processed using immunohistochemistry to label BrdU and NeuN, a neuron-specific protein. We quantified numbers of new neurons in the GCL and striatum. We found that combined male and female DATkd mice had fewer new neurons in the GCL than combined male and female WT mice ($p<0.01$) and a trend toward fewer new neurons in the striatum than WT mice ($p=0.07$). These results suggest that elevated DA independent of receptor manipulation results in a decrease in new neuron proliferation and/or survival.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: NIH R01 AG29493

Title: Vitronectin induces expression of CNTF, LIF and IL-6 which have different effects on adult mouse SVZ neurogenesis

Authors: *C. JIA, M. KEASEY, C. LOVINS, H. MALONE, R. SANTE, V. RAZSKAZOVSKIY, T. HAGG
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Abstract: Vitronectin (VTN) is a plasma protein mainly produced by liver. VTN leaks and accumulates in the brain following injury, which we have shown to induce inflammation through integrin signaling (Keasey SFN 2017). However, the expression and role of endogenous VTN in the naïve brain have not been investigated. Here, we found that mouse subventricular zone (SVZ) expressed a high level of VTN mRNA. VTN protein was uniquely expressed in the pericytes of blood vessels but not in other cells, as shown by confocal microscopy. Intrastriatal injection of recombinant human VTN or plasma from VTN+/+, but not VTN-/-, substantially increased CNTF, LIF and IL-6 expression in the SVZ. Instead of activating integrin signaling, intrastriatal injection of rhVTN unexpectedly inhibited focal adhesion kinase (FAK) in the SVZ and intrastriatal injection of FAK inhibitor induced CNTF, LIF and IL-6. FAK inhibition reduced downstream JNK phosphorylation but increased P38 and ERK phosphorylation. FAK inhibition increased SVZ CNTF via JNK inhibition and ERK activation and enhanced LIF via ERK activation. Inhibition of P38 increased LIF and IL-6. Lastly, we determined the effect of VTN-induced CNTF, LIF and IL-6 on adult mouse SVZ neurogenesis. Intrastriatal injection of rhVTN alone had no effect, possibly because of anti-neurogenic effects of LIF and/or IL-6 through gp130 signaling. Combining injected VTN with the gp130 inhibitor SC144 reduced VTN-induced LIF and IL-6, and, importantly, increased SVZ cell proliferation and neurogenesis as measured by BrdU incorporation and stereological cell counts. This suggests that VTN-induced CNTF promotes SVZ neurogenesis only when LIF and IL-6 expression is suppressed. Injection of the JNK inhibitor, that increased CNTF without altering LIF and IL-6 also increased SVZ neurogenesis via upregulation of CNTF as shown in the lack of effects in CNTF-/- mice, and possibly through FGF2. Taken together, these data suggest that endogenous VTN regulates CNTF, LIF and IL-6 by different intracellular pathways and gp130 inhibition can be used therapeutically to allow CNTF to increase SVZ neurogenesis in naïve mice and possibly following VTN leakage upon brain injury.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

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Topic: A.02. Postnatal Neurogenesis

Title: Role of antioxidant supplementation on sodium arsenite($NaAsO_2$)induced developmental neurotoxicity in rat cerebellum

Authors: *P. DHAR[1], P. KUMAR[2], P. KAUSHAL[1]
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Abstract: Protracted development of the central nervous system (CNS) in the postnatal period is a challenging scenario. Also, the vulnerability of the developing CNS towards various insults increases manifold owing to immature status of blood brain barrier (BBB). Arsenic (*As*), with its ubiquitous distribution in environment, has been reported to induce neurological and behavioral deficits more so following postnatal exposure. Oxidative stress is considered as a major factor underlying *As* induced toxicity. The present study was designed to determine the effects of sodium arsenite ($NaAsO_2$) **e**xposure on apoptosis associated protein profile in rat cerebellum and to evaluate the role of antioxidant (AOX) supplementation on *As* induced adverse effects. Pregnant Wistar rats (19-20 days gestation) were housed under controlled laboratory conditions. The day of delivery of pups was considered as postnatal day zero (PND 0). The pups from different litter groups were randomly assigned to control and experimental groups (n=6/group). The test substances ($NaAsO_2$ alone and $NaAsO_2$ along with ALA/Curcumin) were administered by intraperitoneal (i.p.) route from PND 1 to 21 to experimental groups whereas the control groups received no treatment or only the vehicle. During the experimental period, behavioral tests were carried out and the animals were sacrificed on PND 22.
The cerebellum was processed for immunohistochemical localization of apoptosis associated proteins (Bax and Bcl2), and F1ATPase expression. The preliminary observations are suggestive of AOX induced downregulation of Bax and F1ATPase and upregulation of Bcl2 in rat cerebellum following $NaAsO_2$ exposure, thereby raising the possibility of their beneficial effects as dietary adjuvants, against *As* induced adverse effects.

Disclosures: **P. Dhar:** None. **P. Kumar:** None. **P. Kaushal:** None.

Poster

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Topic: A.02. Postnatal Neurogenesis

Support: BK21 Grant 22A20130012283

NRF Grant 2009-0083538

Title: Neurotoxic effects of acrylamide on the hippocampal neurogenesis and neuronal differentiation

Authors: S. LEE, Y. LEE, W. LEE, *J. LEE
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Abstract: Acrylamide (ACR) has been recognized as a neurotoxic substance to cause cumulative neurotoxicity characterized by ataxia, skeletal muscle weakness, cognitive impairment, and

numbness of the extremities. Previous study showed that high dose ACR impaired hippocampal neurogenesis and increased cell death in neural progenitor cells. However, effects of chronic administration of low dose ACR have not yet been tested on adult neurogenesis and cognitive function. The present study investigated neurotoxic effects of low dose ACR on the hippocampal neurogenesis and neurocognitive function. Mice were administered with vehicle or ACR (2, 20, or 200 μg/kg). No significant changes in the numbers of newly generated cells in the hippocampus administration were observed in ACR-treated mice compared with vehicle-treated. In addition, there were no neuroinflammation and neuronal loss in the hippocampus induced by ACR administration. Further behavioral studies revealed that low doses ACR did not affect any neurocognitive impairments. Interestingly, we found developmental neurotoxicity of ACR in primary cultured neuron, which exposure to ACR during developing stage of primary neuron delayed neuronal differentiation without affecting cell survival. These findings indicated that low dose ACR which are relevant to the exposing levels on a regular basis, might be harmless to affect hippocampal neurogenesis and neurocognitive functions. However there are still potential neurotoxic effects of ACR exposure on developing neurons that could disturb neuronal network.

Disclosures: **S. Lee:** None. **Y. Lee:** None. **W. Lee:** None. **J. Lee:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: National Institute of Allergy and Infectious Diseases grant U19-AI091036

Title: Cranial irradiation leads to sustained deficits in adult hippocampal neurogenesis without reducing neural stem cell count

Authors: *E. BELCHER[1], S. BEGOLLY[2], J. OLSCHOWKA[1], J. WILLIAMS[2], M. K. O'BANION[1]
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Abstract: Cranial radiotherapy is associated with progressive cognitive decline that disrupts quality of life for long-term cancer survivors. Persistent impairment in adult hippocampal neurogenesis (AHN) following cranial irradiation may contribute to post-irradiation cognitive deficits. While many studies report that cranial irradiation leads to sustained deficits in AHN, the impact at the level of neural stem cells (NSCs) is not well-characterized. Additionally, data from other models show that increases in bone morphogenic protein 6 (BMP6) contribute to persistent deficits in AHN by inhibiting NSC division. **We hypothesize that NSCs survive cranial irradiation, but that a long-term increase in BMP6 activity impairs NSC division.** 8-10

week-old C57BL/6 mice received 0, 2, 8, or 20Gy cranial irradiation using a ^{137}Cesium gamma source. Mice were sacrificed 6 h, 3 d, 6 m and 18 m after irradiation. Immunohistochemistry was used to quantify doublecortin-positive neuroblasts, BrdU-positive proliferating progenitors, and nestin-positive NSCs in the hippocampal dentate gyrus. Activated caspase-3 was also analyzed to quantify apoptosis. Our results confirm that cranial irradiation acutely depletes neural progenitor cell populations via apoptosis. Interestingly, we found that cranial irradiation did not kill NSCs. Furthermore, while neurogenesis remained impaired up to 18 months following cranial irradiation, the NSC population size was equivalent to sham-irradiated controls. Indeed, age-related decreases in NSC count were not exacerbated by cranial irradiation. These data support our hypothesis that NSCs survive irradiation but their division is impaired, suggesting a therapeutic strategy aimed at stimulating NSC division. Additionally, we found by RT-qPCR that BMP6 mRNA was elevated in whole brain homogenates 6 h post-irradiation. Our ongoing studies will test the hypothesis that BMP inhibitor Noggin will promote NSC division and rescue AHN post-irradiation. These results shed light on how cranial irradiation leads to long-term deficits in neurogenesis, and may contribute to future development of targeted therapies to mitigate cognitive decline following cranial radiotherapy. *This work was supported by the National Institute of Allergy and Infectious Diseases grant U19- AI091036.*

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: Marsden Fund of the Royal Society of New Zealand

Title: Dormant adult-born neurons can be activated by exposure to an enriched environment

Authors: *S. M. OHLINE[1,3,4], R. U. HEGEMANN[1,3], K. L. WAKE[1,3], M. F. DINNUNHAN[1,3], L. SCHWEITZER[3,4,1,2], S. M. HUGHES[2,3,4], W. C. ABRAHAM[1,3,4]
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Abstract: Neurogenesis occurs throughout adulthood in mammals. We have shown that dentate gyrus granule cells show evidence of cell-age dependent “retirement” when born in adulthood but not when born during adolescence, for standard-home caged (HC) male Sprague-Dawley rats. To reveal this, we “birth-dated” newly born granule cells using dual labelling with two thymidine analogues, (chloro-deoxyuridine (CldU) and iodo-deoxyuridine (IdU)), given at 35,

12, 6 or 4 weeks prior to study for animals 10 months of age. One hour before death, all animals were exposed to a novel environment for 5 minutes. We then used double-label immunofluorescence to identify active neurons as indicated by co-localization of the thymidine analogue with expression of the immediate early gene Egr1, and found that activity declined across 4-12 weeks as cells matured, as expected, but that 35 wk-old cells (born during adolescence, i.e. in animals 2 mo of age) were as excitable as 4 wk-old cells, particularly in the dorsal hippocampus. Here, we sought to determine whether the cell-age dependent decline in activity in adult-born cells would be counteracted by exposing rats to an enriched environment (EE) for ten nights just prior to study at 10 months of age. We found that EE exposure caused an overall increase in granule cell activity compared to home-cage controls ($F_{(3,31.0)} = 3.541$, $p = 0.026$). This changed the pattern of cell-age dependency, such that while 4 wk-old cells remained the most excitable age group (Egr1+/XduU+ = 6.6 ± 1.18%), the 6 and 12 wk old cells increased excitability to the level of the 35 wk-old EE cells (Egr1+/XdU+ = 2.5 ± 0.97%). This change in pattern was most evident in the dorsal hippocampus, although the ventral hippocampus did exhibit the overall increase in granule cell activity from EE treatment ($F_{(1, 20.1)} = 5.64$, $p = 0.03$). Overall, we found that EE increased activity of adult-born granule cells relative to that of HC animals, except at the 35 week time point. We suggest that this is likely due to the HC animals finding the novel environment exposure before death particularly salient, and that cells born during adolescence retain a privileged level of excitability compared to younger cells that were born during later adulthood. However, EE exposure equalises the activity level of mature granule cells regardless of the animal age at their birth, leaving only the young 4 wk old cells as being relatively more excitable than the others. These increases in granule cell excitability may contribute to the cognitive gains afforded by enriched environments. Supported by the Marsden Fund Council, administered by the Royal Society of New Zealand.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.20/B28

Topic: A.02. Postnatal Neurogenesis

Support: UMMC Pediatric Discovery Council Research grant

Title: Intrauterine growth restriction as factor in long-term neurobehavioral outcome of neonatal hypoxic ischemic injury in a rodent model

Authors: *R. NARANG[1,1], K. CARTER[2], C. MUNCIE[2], Y. PANG[5], L.-W. FAN[1], Y. FENG†[6], N. OJEDA[3], A. J. BHATT[4]

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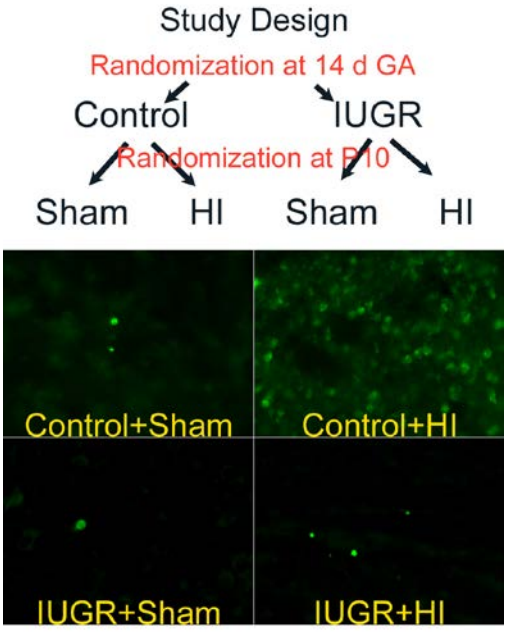
Abstract: There is a lack of knowledge of factors preventing adequate response to moderate hypothermia after hypoxic ischemic (HI) brain injury. We hypothesized that growth restriction from reduced intrauterine perfusion would predispose neonatal rats to have worse outcome with HI brain injury.

IUGR was induced by placental insufficiency in dams at 14 days of gestation. HI was induced at postnatal day (P) 10 by permanent right carotid artery ligation followed by 90 min of hypoxia (8% oxygen). Tests for early brain injury and neurobehavioral outcomes were subsequently done. All statistical analysis was done using Two-way ANOVA; post hoc Holm-Sidak test.

HI in control and IUGR groups decreased the success rate of the contralateral vibrissa-elicited forelimb test, increased response latency in movement initiation test and increased the time to finish elevated beam walk test at P40 and P60 ($p<.05$, n=8-12). IUGR augmented HI induced abnormality in vibrissa-elicited forelimb test at P40 but showed higher success rate when compared to HI only group at P60 ($p<.05$, n=8-12).IUGR's negative effect on elevated beam walk test was sex –specific and exaggerated in P60 males. Early brain injury was seen in IUGR and HI with increased caspase-3 activity in right cortex (P= <0.05, n= 3-5 pups) that was further increased in IUGR+HI (p= <0.05, n=3-5). Increased TUNEL positive cells in cortex were noted at 72 h after in HI in control but not in IUGR groups (P= <0.001, n=7).

This study provides evidence that IUGR worsened HI-induced gross motor abnormality in male rats, IUGR differentially effects sensory-motor outcomes with worsening at P40 but improvement at P60 with no sexual dimorphism. IUGR increased HI induced early brain injury at 24 h but the evidence was not seen at 72h.



TUNEL positive cells in Cortex at 72 h after HI

Disclosures: **R. Narang:** None. **K. Carter:** None. **C. Muncie:** None. **Y. Pang:** None. **L. Fan:** None. **Y. Feng†:** None. **N. Ojeda:** None. **A.J. Bhatt:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.21/B29

Topic: A.02. Postnatal Neurogenesis

Support: NSERC Discovery Grant

NSERC PGSD

Killam Doctoral Scholarship

Title: Testing the limits of adult neurogenesis: Optimizing neurogenic treatments for sustained efficacy

Authors: *J. COLE[1], ***J. COLE**[1], S. P. CAHILL[2], R. YU[3], J. CLEMANS-GIBBON[4], J. S. SNYDER[5]
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Abstract: Immature adult-born neurons are physiologically distinct from older neurons and contribute to the mnemonic and emotional functions of the hippocampus. Methods for increasing neurogenesis therefore have the potential to improve improve mental health in a number of conditions such as Alzheimer's disease, depression and schizophrenia, all of which are associated with hippocampal structural deficits. Most studies have only examined single methods for short-term elevations of neurogenesis, which may be insufficient to offset major structural changes. The present study therefore examined whether two well known neurogenic treatments, running and the NMDA receptor antagonist memantine, are capable of producing sustained increases in adult neurogenesis. To identify whether there are sex differences in regulation of neurogenesis, both male and female rats were examined. We found that, on their own, both treatments increased adult neurogenesis but levels returned to baseline one month later. To optimize treatments for prolonged elevation of neurogenesis rats were subjected to 8 weeks of running, 8 weeks of memantine, or two alternating 4-week blocks of each treatment and compared to cage controls. PCNA and doublecortin (DCX) were used to quantify proliferating cells and immature neurons, respectively, that were present at the end of treatment. In males, single treatments failed to increase numbers of proliferating cells and immature neurons. However, memantine followed by running increased proliferating cells, and running followed by

memantine increased the number of immature neurons. In females, there was a trend for increased numbers of proliferating cells and immature neurons after 8 weeks of running, possibly because they ran significantly more than males. The thymidine analogs CldU and IdU were used to label neurons born at the beginning of each 4-week treatment block. Preliminary analysis of CldU+ neurons born during the first treatment block suggest that in males, but not females, cells born during initial memantine treatments survive to a greater extent when followed up with running. Analyses of IdU+ cells, born during the second treatment block, are currently underway. We are also quantifying putative neural stem cells to determine why some treatment paradigms lead to sustained increases in neurogenesis but others do not. Collectively, our data suggest that there may be limitations in the extent to which single treatments can enhance adult neurogenesis. Instead, a combination of approaches may be more effective and, moreover, may vary between males and females.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.22/B30

Topic: A.02. Postnatal Neurogenesis

Support: R56MH106809

R01MH091844

Title: Transient inhibition of neural stem cell proliferation during early life alters adult dentate gyrus stem cell pool and neurogenic lineage

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Abstract: Early life stress has been shown to increase vulnerability to psychiatric illness in adulthood. The hippocampal dentate gyrus (DG) is altered by stress and plays a role in stress regulation. The DG is also one of the two brain regions in which neural stem cells give rise to neurons throughout an animal's life, a process that is negatively regulated by stress. In this study, we sought to determine whether inhibition of neurogenesis during critical developmental periods is sufficient to permanently decrease DG neurogenesis. We used a pharmacogenetic approach to

transiently target dividing neural stem cells for elimination by administering the drug valganciclovir to GFAP-Tk mice during periods sensitive to stress. We then assessed the Nestin neural stem cell lineage in adulthood. We found a reduction in the number of neural stem cells and their neuronal progeny in adult animals following a transient targeting of stem cells during the neonatal period. In contrast, similarly targeting stem cells around the time of weaning resulted in decreased neurogenesis without permanently diminishing the adult stem cell pool. This study highlights two sensitive periods during which brief suppression of stem cell proliferation results in distinct and enduring consequences for the adult neural stem cell system. It is intriguing to speculate that infantile neurogenesis serves as a cellular target for the enduring effects of stress.

Disclosures: M. Youssef: None. **G. Kirshenbaum:** None. **V. Krish:** None. **E.D. Leonardo:** None. **A. Dranovsky:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Topic: A.02. Postnatal Neurogenesis

Support: NIH Grant K99 MH108719-01

NIH Grant R37 MH068542

HDRF MPPN8883

NYSTEM

DFG

Title: Adult hippocampal neurogenesis buffers ventral dentate gyrus responses to chronic stress

Authors: *C. ANACKER[1], G. STEVENS[1], A. MILLETTE[1], R. SHORES[1], R. HEN[2]
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Abstract: Adult hippocampal neurogenesis has been proposed to confer resilience to chronic stress and to modulate dentate gyrus activity. However, it is unknown how adult-born neurons regulate information processing in the dentate gyrus granule cell network. Here, we used *in vivo* Ca^{2+}-imaging with head-mounted miniature microscopes (Inscopix, CA) in the dentate gyrus of freely moving mice to investigate how young adult-born neurons regulate the response of mature granule cells during chronic psychosocial stress.
The intracellular Ca^{2+} indicator, GCamp6f, was virally-expressed in mature granule cells of the

ventral dentate gyrus. Ca^{2+} activity was imaged in wild-type mice with normal levels of neurogenesis and in transgenic mice with a 2±0.2 fold increase in doublecortin-positive young neurons, due to a deletion of the pro-apoptotic gene *Bax* from adult neural stem cells and their progeny. We imaged 30-100 granule cells per mouse throughout 10 days of social defeat stress and during subsequent tests of anxiety-like behavior.
On the first day of social defeat, granule cells of the ventral dentate gyrus do not respond to an attack by a dominant aggressor mouse. However, Ca^{2+} firing rates are overall higher in wild-type mice with normal levels of neurogenesis (0.01±0.001, n=548 cells) than in mice with increased neurogenesis (0.008±0.001, n=540 cells, p=0.03). On the last day of the social defeat stress procedure (day 10), wild-type mice show increased Ca^{2+} activity in response to an attack (0.017±0.001, n=548 cells). This effect is reduced in mice with more neurogenesis (0.013±0.0006, n=540 cells, p=0.02). After chronic social defeat, mice with increased neurogenesis are resilient to the stress and interact longer with a novel mouse in a social interaction test than wild-type mice (by 35±4%; n=10 mice; $p<0.01$). These resilient mice with more neurogenesis also exhibit lower granule cell Ca^{2+} firing rates during social interaction than wild-type mice (by 23±1%; p=0.05). In the open field test, mice with increased neurogenesis spend more time in the brightly lit anxiogenic center of the open field than wild-type mice (40±5% sec; n=10 mice, $p<0.05$). Ca^{2+} firing rates are higher during center exploration than during exploration of the less anxiogenic periphery (periphery rate: 0.010±0.0003; center rate: 0.014±0.0007, n=548 cells, p=0.002). However, mice with increased neurogenesis exhibit lower center rates than wild-type mice (0.008±0.0008, n=540 cells, $p<0.0001$).
Our findings demonstrate that hippocampal neurogenesis inhibits the response of ventral dentate gyrus granule cells to chronic stress and to anxiogenic conditions.

Disclosures: C. Anacker: None. **G. Stevens:** None. **A. Millette:** None. **R. Shores:** None. **R. Hen:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.24/B32

Topic: A.02. Postnatal Neurogenesis

Support: NIH NIAAA P50AA022534

NIH NIAAA Administrative/Diversity Supplement 3P50AA022534-03S1

Title: Acute and long-term effects of early postnatal alcohol exposure on hippocampal neurogenesis in mice

Authors: *K. C. GUSTUS, V. LOPEZ, J. NEWVILLE, P. TAPIA, L. LI, C. F. VALENZUELA, L. A. CUNNINGHAM
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Abstract: Fetal alcohol spectrum disorders (FASDs) have been associated with reduced hippocampal volume and impairments in hippocampal-dependent tasks (Autti-Rämö et al., 2002; Parnell et al., 2009; Allan et al., 2003). Using a limited access mouse model of gestational alcohol exposure, we previously demonstrated impaired hippocampal neurogenesis in response to environmental enrichment (Choi et al., 2005; Kajimoto et al., 2013). In the present study, we investigated the acute and long-term impact on hippocampal neurogenesis following third trimester equivalent ethanol exposure, the time period during which granule cells of the developing dentate gyrus are most rapidly generated. At postnatal day (PD)2 male Nestin-CreER^{T2}:tdTomato mouse pups received an injection of tamoxifen (33mg/kg i.p.) to induce expression of tdTomato reporter in all nestin+ hippocampal progenitors and their downstream progeny. Following tamoxifen administration, cages containing both mother and pups were placed into ethanol or air (control) vapor chambers where they were exposed to ethanol vapors or air for 4 hours per day from PD3-15 (average pup blood ethanol concentration, BEC=160.4±12.0 mg/dl; range 128.2-185.6 mg/dl). tdTomato+ DGCs were quantified using confocal stereology at PD16 and PD50. Alcohol had no significant impact on the number of tdTomato+ DGCs at either time point: acute (PD16 air: 3.021e5±0.6074e5 cells/mm^3 n=4, etoh: 3.36e5±0.7446e5 cells/mm^3 n=3 p=0.7366) and long-term (PD50 air: 3.655e5±0.3246e5 cells/mm^3 n=4, etoh: 3.692e5±1.314e5 cells/mm^3 n=3 p=0.9802). These findings suggest resistance of newly generated DGCs to acute ethanol toxicity during third trimester equivalent exposure, and no long-term impairment of hippocampal neurogenesis when mice are reared under normal housing conditions. Experiments are currently underway to determine whether this exposure paradigm impairs the neurogenic response to enriched environment.

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Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Program#/Poster#: 115.25/B33

Topic: A.02. Postnatal Neurogenesis

Support: NIH/NIAAA Grant R37AA007789 to JW

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NeuroDevNet 20R64153 to JW

CIHR MOP142308 to LAMG

NSERC CGSM to SLB

Aboriginal Graduate Fellowship to SLB

Title: Neurogenic, neuroendocrine, and behavioural outcomes following prenatal alcohol exposure: Modulation by oxytocin

Authors: *S. BAGLOT[1], C. FUNG[1], P. UBI[1], E. MORGAN[1], S. E. LIEBLICH[2], W. YU[1], L. A. M. GALEA[2], J. WEINBERG[1]
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Abstract: Fetal alcohol spectrum disorders encompasses a group of diagnoses characterized by a range of cognitive, physiological, behavioural, and emotional deficits. Of particular relevance to this study, prenatal alcohol exposure (PAE) leads to persistent alterations in emotional regulation and stress system response (i.e. hypothalamic-pituitary-adrenal [HPA] axis). The hippocampus (HPX), a brain area sensitive to teratogenic effects of alcohol, is involved in stress and emotional regulation; specifically, neurogenesis occurs in the HPX into adulthood and is implicated in these functions. HPX neurogenesis is altered following PAE and thus may be one mechanism by which HPA dysregulation and emotional deficits occur following PAE. Oxytocin (OT), a neuropeptide implicated in stress and emotional regulation, has been shown to stimulate HPX neurogenesis and dampen HPA axis activity in male rats. However, it remains unknown whether modulatory effects of OT occur in females or following PAE. Utilizing an animal model we examined the possible role of OT in modulating the effects of PAE on HPX neurogenesis, HPA axis functioning, and expression of anxiety-like behaviours. In adulthood, male and female offspring from PAE, pair-fed, and control dams were treated daily with OT (0.5mg/kg or 1mg/kg) or vehicle for 10 days. HPA axis activity was measured through corticosterone (CORT) levels before and after 30 min restraint stress. Anxiety-like behaviour and activity was examined in the novelty suppressed feeding (NSF) task. HPX neurogenesis was measured through expression of doublecortin. NSF data indicate PAE males exhibited a shorter latency to feed, indicating less anxiety or more motivation for food, while females show no differences. Notably, OT significantly decreased locomotor activity in both sexes, though in a prenatal condition and OT dose dependent manner: male controls responded at the higher dose while PAE responded at the lower dose. This OT dependent decrease in activity may have greater implications for PAE animals, which display hyperactivity compared to controls. CORT levels suggest a possible role for OT in facilitating recovery of the stress response following restraint in both sexes. Preliminary data suggests that, similar to NSF and stress response, HPX neurogenesis is affected. Overall, our data reveal a possible role of OT in decreasing hyperactivity and facilitating stress recovery following PAE.

Disclosures: S. Baglot: None. **C. Fung:** None. **P. Ubi:** None. **E. Morgan:** None. **S.E. Lieblich:** None. **W. Yu:** None. **L.A.M. Galea:** None. **J. Weinberg:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.26/B34

Topic: A.02. Postnatal Neurogenesis

Title: High levels of cell proliferation on postnatal spinal cord and hippocampus in fluoxetine hydrochloride-treated mice: An in-vivo study

Authors: *N. GHANI[1,2], I. KEARNS[1], A. VAN DER SCHOOT[1], J. DEUCHARS[1], S. A. DEUCHARS[1]
[1]Sch. of Biomed. Sci., Univ. Of Leeds, Leeds, United Kingdom; [2]Sch. of Dent. Sci., Universiti Sains Malaysia, Health Campus Kubang Kerian, Malaysia

Abstract: The central canal area has been found to be a neurogenic niche, with ependymal cells having the characteristics of self-renewal, multilineage capability and clonogenic efficiency. However the ability of certain neurotransmitters to control cell proliferation is still unknown. To determine the effect of endogenous serotonin on cell proliferation of spinal cord, C57BI/6 mice (6-8 week, n=4) were injected with fluoxetine hydrochloride (Flx) in 10 mg/kg for 10 days and the thymidine analogue 5-ethynyl-2'-deoxyuridine (EdU) in 10 mM was injected for the last 5 days to determine the extent of cell proliferation. The control group C57BI/6 (6-8 week, n=4) were injected with saline and EdU for 10 days and the last 5 days respectively. The mice were anaesthetized (60 mg/kg sodium pentobarbitone) and perfused transcardially with 4% paraformaldehyde. Thoracolumbar spinal cord and hippocampal regions were removed and sectioned (50 µm) and detection for EdU was performed. EdU+ve cells were counted in central canal, grey matter and white matter of the spinal cord. Flx-treated mice showed a significantly higher level of cell proliferation in specific regions of spinal cord compared with the control group. In total thoracolumbar grey matter, there were significantly more proliferating cells in mice treated with Flx compared with control (28.5±1.1 vs 24.8±1.03 cells/50 µm section, $p<0.05$). This was due to a specific difference at thoracic (26.6±1.6 vs 21.8±1.3, $p<0.05$) rather than lumbar levels. However there were no significant differences in the numbers of EdU+ve cells between Flx-treated and control mice in either the central canal or white matter. Since the majority of EdU labelling in the grey matter was confined to the dorsal horn, we examined the effects of Flx in this region and noted a significantly higher number of EdU+ve cells in the dorsal horn at thoracic levels (15.3±1.4 vs 10.0±0.8, $p<0.05$). As a positive control, in dentate gyrus there were significantly greater numbers of EdU+ve cells (50.0 ± 2.2 cells per field of view) compared to the control group (30.7 ± 3.0). These results showed that Flx can influence cell proliferation in a regional specific manner. This indicated the influence of endogenous serotonin in promoting high levels of cell proliferation since fluoxetine blocks the serotonin transporters, increasing serotonin levels in the synaptic cleft.

Disclosures: **N. Ghani:** None. **I. Kearns:** None. **A. Van der Schoot:** None. **J. Deuchars:** None. **S.A. Deuchars:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.27/B35

Topic: A.02. Postnatal Neurogenesis

Title: Neurotoxic effect of cannabinoid receptor agonists in neonatal rats

Authors: *M. HUIZENGA, A. UME, P. FORCELLI
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Abstract: Neonatal seizures and seizures of infancy represent a significant cause of morbidity. 30-40% of infants and children with seizures will fail to achieve seizure remission with current anti-epileptic drug (AED) treatment. Moreover, pharmacotherapy during critical periods of brain development can adversely affect nervous system function. We, and others, have shown that early life exposure to AEDs including phenobarbital, phenytoin, and valproate are associated with induction of enhanced neuronal apoptosis during a confined period of postnatal development in rats. Thus, identification of new therapies for neonatal/infantile epilepsy syndromes that provide seizure control without neuronal toxicity is a high priority.
Following reports that drugs targeting the cannabinoid system (e.g., CB1 receptor agonists) display anticonvulsant efficacy in adult animal models of seizures/epilepsy, they remained unexplored in neonatal models. We were among the first to systematically investigate the therapeutic potential of these drugs in neonatal rodent seizure models, reporting anticonvulsant effects with both a CB1/2 mixed agonist (WIN 55,212-2) and CB1 agonist (ACEA) in postnatal day 10 (P10) animals. However, the potential neurotoxic effect of these drugs during development remains to be seen.
Therefore, WIN 55,212-2 and ACEA were administered at our previously reported therapeutic doses, to the developmentally sensitive P7 rat pups and neuronal cell death was examined 24 hours post-treatment. Fluoro-Jade B staining was used to label apoptosis in several brain regions including: cingulate cortex, striatum, lateral septum, and nucleus accumbens. We found that despite exerting anti-seizure effects in P10 neonates, both cannabinoids induce neuronal apoptosis above DMSO control levels.
Together, these results indicate that during a developmentally sensitive neonatal period, drugs targeting the cannabinoid system induced neuronal apoptosis in a CB-receptor dependent manner. These data provide further need for the evaluation of new therapies for neonatal epilepsies that exert seizure control without increasing apoptosis of the developing brain.

Disclosures: **M. Huizenga:** None. **A. Ume:** None. **P. Forcelli:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.28/B36

Topic: A.02. Postnatal Neurogenesis

Support: NSERC 2016-04695

Title: Developmental effect of cannabinoids exposure during gastrulation in zebrafish

Authors: *M. AMIN, K. T. AHMED, D. W. ALI
Biol. Sci., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Cannabis is one of the oldest and the world's third most popular recreational drug, after alcohol and tobacco. Several studies indicate that cannabis use during pregnancy is increasing due to the fact that it is easily accessible and is considered to be relatively harmless. It is reported that about six percent of pregnant females aged between 12 to 44 have used cannabis during their first trimester. Epidemiological studies have revealed that the negative impact of prenatal cannabis use continues into later stages of life- such that children exhibit neurocognitive deficits, aggressive behavior and attention disorders. THC (Δ9-tetrahydrocannabinol) is the major psycho-active component of marijuana while CBN (cannabinol) is a non-psycho-active oxidative metabolite of THC. In this study, we sought to investigate the effect of THC and CBN on developing embryos using zebrafish as a model organism. We exposed zebrafish embryos to THC and CBN only during the 5-hour gastrulation stage. Our findings showed that both THC and CBN exposure during gastrulation have detrimental effects on the developing embryo. Embryonic survival was significantly reduced by CBN but not THC exposure. Both compounds delayed hatching and reduced body length by 2 days post fertilization (dpf). Embryos exposed to CBN exhibited dramatic malformations along their body axis. Interestingly, we also observed as much as a 50% reduction in heart rate in embryos exposed to THC and CBN. We performed qPCR to determine the relative levels of mRNA coding for the CB1 and CB2 receptors in zebrafish embryos and found that the both CB1 and CB2 are present during gastrulation and that exposure to THC downregulates CB1 and CB2 receptors by 2 dpf. We also examined effects on cells involved in locomotion. We found that exposure to cannabinoids altered the morphology and branching patterns of primary and secondary motor neurons. Additionally, the morphology of the Mauthner neurons was also altered. Findings from locomotor studies revealed that escape response parameters (angle and time to C-bend) were significantly affected by exposure to THC and CBN. Exposure to cannabinoids also altered muscle fiber morphology. Recording of spontaneous currents (mEPCs) both from THC and CBN exposed white muscle fibers showed that the mEPC frequency was decreased, and the mEPC amplitude was increased significantly

compared to control. Taken together, our findings reveal that brief exposure to cannabinoids, only during gastrulation, causes severe developmental defects in zebrafish embryos.

Disclosures: **M. Amin:** None. **K.T. Ahmed:** None. **D.W. Ali:** None.

Poster

115. Postnatal Neurogenesis: Environmental and Pharmacological Modification

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 115.29/B37

Topic: A.02. Postnatal Neurogenesis

Support: Stony Brook University

Title: Seasonal effects on adult neurogenesis in turtles

Authors: *A. S. POWERS, A. AYANRU, S. BOYD, M. CHANG, A. CULOSO, J. ENG, K. HANINGTON, B. HANUSCH, W. R. KOCHEN, C. LOWE, E. MCLAUGHLIN, A. THOMPSON, A. WALSH, S. WONG, C. YU
Psychology, Stony Brook Univ., Stony Brook, NY

Abstract: Seasonal effects on adult neurogenesis have been reported in many species of reptiles. The effects vary greatly from species to species (Powers, 2016), but no data have been reported for turtles. In experiments intended to study environmental influences on adult neurogenesis, we discerned seasonal effects. We studied western painted turtles (*Chrysemys picta*), which were obtained from a supplier in Florida. The turtles were used in three different experiments investigating enriched environments, maze learning, and discrimination learning. The results of these experiments will be reported elsewhere.
In all three experiments, turtles were given 9 injections of BrdU (50 mg/kg), 3 times per week for 3 weeks. In the enriched environment experiment, the animals were euthanized either 1 day, 3 weeks, or 6 weeks after the last BrdU injection. In the other two experiments, all animals were euthanized 3 weeks after the last BrdU injection. We attempted to prevent seasonal effects by maintaining the animals in a constant environment: no natural light, constant temperature (29 degrees C.), and a constant day/night cycle of 14 h light/10 h dark. The diet of the animals varied across experiments but consisted of either pellets manufactured for aquatic turtles (Mazuri) or beef baby food (Beechnut). In all three experiments, we ran multiple replications at different times of year.
We counted the total number of BrdU-positive cells in the telencephalon in 14 sections representing different anterior-posterior levels, in 54 turtles. In all three experiments, when the data were combined across treatments, we found that turtles run in the summer showed more BrdU-positive cells than those run in the spring or fall. This finding was surprising given the variety of different treatments we used and the effort to prevent seasonal changes from affecting

the turtles. Hypothesizing that the time of shipping of the turtles from the supplier would predict number of cells, we found that turtles shipped between February and June had the greatest number of new cells. Neither weight nor sex was correlated with number of total new cells. At the present time, we do not know whether the seasonal effects we observed were due to the season in which the turtles were shipped by the supplier or the season in which they were run, but the season of shipping seems more likely because the lab environment was kept constant. Some animals were kept in the lab for as long as 18 months before being used in an experiment, however, and such a result would suggest that they retained some seasonal rhythm from the wild for that considerable length of time.

Disclosures: **A.S. Powers:** None. **A. Ayanru:** None. **S. Boyd:** None. **M. Chang:** None. **A. Culoso:** None. **J. Eng:** None. **K. Hanington:** None. **B. Hanusch:** None. **W.R. Kochen:** None. **C. Lowe:** None. **E. McLaughlin:** None. **A. Thompson:** None. **A. Walsh:** None. **S. Wong:** None. **C. Yu:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.01/B38

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant MH084989-08A1

Title: FMRP is required for critical period sensory input plasticity in the *Drosophila* olfactory circuit

Authors: *R. M. GOLOVIN, J. VEST, K. BROADIE
Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: Rational: FMRP is known to control developmental plasticity within antennal lobe projection neurons during an early-use critical period, however it is not known whether FMRP loss alters plasticity within the antennal lobe circuit. The goal of this work is to uncover how developmental odor exposure reorganizes the antennal lobe and how FMRP regulates this process. We are testing 3 non-mutually exclusive hypotheses: 1) FMRP controls activity-dependent translation of core signaling factors (e.g Notch and Wingless). 2) FMRP sets the excitatory/inhibitory balance enabling odor-dependent developmental plasticity. 3) FMRP control membrane trafficking during activity-dependent changes important for the growth and refinement of synaptic connections.
Methods: In order to test how critical period odor exposure affects the development of sensory neurons, we are investigating morphological, functional and behavioral changes in staged animals exposed to odorants. Connectivity changes are being assessed using membrane and

synaptic markers expressed in Or42a (VM7) and Or85a (DM5). Functional changes associated with critical period odor exposure are being measured with transgenic calcium/chloride fluorescent reporters and patch-clamp electrophysiology. Behavioral changes are being analyzed using odor discrimination assays. Genetic background controls are compared to loss-of-function FMRP mutants. Targeted RNAi-mediated knockdown in sensory and projection neurons, as well as targeted manipulation of circuit activity using optogenetic tools, are being used to test of the role of regulatory proteins, activity and membrane trafficking in FMRP-dependent critical period plasticity.
Results: The data to date shows that after odorant exposure during the critical period Or42a OSNs exhibit a significant reduction in glomerulus volume. Conversely, Or85a OSNs show an opposite phenotype of expanded volume following critical period odorant exposure compared to the vehicle. These odorant-dependent changes during the critical period are lost in *dfmr1* null mutants in both Or42a and Or85a neurons, showing that FMRP is important for both bidirectional changes. This plasticity is restricted to the critical period of early sensory input closely following eclosion .
Conclusions: These results show that the loss of FMRP can reduce activity-dependent critical period synaptic plasticity bidirectionally within the same sensory circuit. Our ongoing research focusses on linking anatomical plasticity to functional and behavioral changes, as well as testing different aspects of FMRP function in driving critical period plasticity during neural circuit refinement.

Disclosures: R.M. Golovin: None. **J. Vest:** None. **K. Broadie:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Priority Program 1665 of the German Research Foundation

Collaborative Research Centre/Transregio 166 of the German Research Foundation

Title: Somatostatin-positive GABAergic interneurons contribute to neuronal network activity in the developing mouse hippocampus

Authors: *T. FLOßMANN, K. KIRMSE, O. W. WITTE, K. HOLTHOFF
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Abstract: Synchronized spontaneous network activity represents a characteristic property of immature neural networks and is thought to contribute to their developmental refinement. In the

developing hippocampus *in vitro*, synchronized activity in the form of so-called giant depolarizing potentials (GDPs) strongly depends on the depolarizing action of $GABA_A$ receptor activation. However, the contribution of distinct subpopulations of GABAergic interneurons remains incompletely understood. In the present study, we addressed whether somatostatin-positive (SOM) GABAergic interneurons participate in the GABAergic control of GDP generation. In agreement with previous data, confocal Ca^{2+} imaging experiments revealed that GDPs were strongly attenuated by acute pharmacological inhibition of the chloride importer NKCC1. Optogenetic activation of SOM interneurons using Channelrhodopsin 2 (H134R) induced $GABA_A$-receptor dependent postsynaptic currents in CA1 pyramidal cells already at postnatal day 1. In the presence of ionotropic glutamate receptor antagonists, local photoactivation of SOM interneurons evoked action potential firing in a considerable fraction of CA1 pyramidal cells. Furthermore, Ca^{2+} imaging data showed that photoactivation of SOM interneurons could induce GDP-like network events which were strongly attenuated by NKCC1 inhibition. Collectively, the present data support the view that SOM interneurons may facilitate neuronal synchronization in the developing hippocampus.

Disclosures: **T. Floßmann:** None. **K. Kirmse:** None. **O.W. Witte:** None. **K. Holthoff:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.03/B40

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant K01MH107760

Sackler Foundation Fellowship

Brain and Behavior Research Foundation Young Investigator Award

Title: Developmental origins of adult prefrontal cortical PV interneuron functional dysconnectivity

Authors: *S. E. CANETTA[1], E. TEBOUL[2], A. S. BROWN[2], C. KELLENDONK[1]
[1]Div. of Mol. Therapeut., Columbia Univ., New York, NY; [2]New York State Psychiatric Inst., New York, NY

Abstract: Abnormalities in prefrontal cortical parvalbumin-expressing (PFC PV) interneurons are believed to contribute to cognitive and affective deficits in schizophrenia (SCZ), as well as other neurodevelopmental psychiatric disorders. However, little is known about whether developmental alterations in PV inhibitory interneuron maturation and integration into cortical circuitry could be contributing to disease onset.

We have recently shown that mice exposed to an early environmental risk factor for SCZ—prenatal maternal immune activation (MIA)—show decreased functional inhibitory connectivity between PFC PV interneurons and pyramidal cells in adulthood, and that these physiological changes result in impairments in cognitive flexibility and anxiety. Therefore, we decided to utilize this model to investigate changes in PFC PV interneuron function during development that may precede and precipitate these long-term functional and behavioral alterations observed in the adult.
We discovered that PFC PV interneurons in MIA offspring show decreased intrinsic excitability transiently during early development, corresponding to a window when extensive pruning of synaptic connections is known to occur. This change in excitability appears due to an increase in an inward conductance active around resting membrane potential and at more hyperpolarized potentials in PFC PV interneurons. Our ongoing studies now aim to understand whether these transient changes in PFC PV interneuron excitability early in development are sufficient to induce the long-term changes in PFC PV interneuron functional connectivity observed in adult MIA offspring. To this end we have used the designer chemogenetic receptor, hM4D, and its exogenous ligand, CNO, to transiently decrease excitability in developing PFC PV interneurons between P21 and P50—encompassing the early window in which we observe transiently decreased excitability in MIA PFC PV interneurons. Our electrophysiological studies at P52—two days following the end of this transient manipulation—revealed that there were fewer spontaneous inhibitory synaptic currents in PFC pyramidal cells, consistent with the idea that the excitability of PFC PV cells during development may determine their synaptic connectivity later in life. Ongoing studies are examining the effect of this transient developmental manipulation on the strength of GABAergic inhibition in adulthood, as well as behavior.

Disclosures: **S.E. Canetta:** None. **E. Teboul:** None. **A.S. Brown:** None. **C. Kellendonk:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

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Program#/Poster#: 116.04/B41

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Grants-in-Aid for Scientific Research (21220006 and 25000015 to M.K.; 23700393 and 16K19672to M.N.; 24220007 to M.W.; and 23500400, 26290010, 15H01667, and 16H01344 to M.M.) from JSPS, Japan

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The Brain Science Foundation

The Takeda Science Foundation

Title: The metabotropic glutamate receptor subtype 1 mediates visual-experience dependent maintenance of synaptic connectivity in the dorsal lateral geniculate nucleus

Authors: *M. NARUSHIMA[1,2], M. UCHIGASHIMA[3], Y. YAGASAKI[4], T. HARADA[5], Y. NAGUMO[4], N. UESAKA[6], K. HASHIMOTO[7], A. AIBA[5], M. WATANABE[3], M. MIYATA[4], M. KANO[6]

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Abstract: Neuronal connectivity have to be maintained stably for proper brain function after initial synapse formation and subsequent refinement during development. In the dorsal lateral geniculate nucleus (dLGN) of mice, synapses from retinal ganglion cell axons onto thalamocortical neurons (retinogeniculate synapses) are established through three distinct phases, namely map formation, synapse elimination, and experience-dependent maintenance. At the maintenance phase that starts around postnatal day 20 (P20), retinogeniculate synaptic connectivity is maintained in a visual experience-dependent manner because one week of dark rearing from P20 (late DR) causes abnormal remodeling of those synapses. A few molecules such as MeCp2 have been reported to be involved in the maintenance phase (Noutel et al., 2011) but further mechanisms were unclear. In this study, we found that experience-dependent maintenance of retinogeniculate synapses was critically dependent on the metabotropic glutamate receptor subtype 1 (mGluR1). Expression of mGluR1 in the dLGN was low before eye-opening (P10) then clearly increased from P15 by the beginning of the maintenance phase (P20). In mGluR1 knockout (mGluR1-KO) mice, synapse formation and elimination occurred normally until around P20 but weak retinogeniculate synapses were newly recruited during the subsequent maintenance phase. This remodeling was similar to those of wild-type (WT) mice that underwent late DR. By contrast, late DR of mGluR1-KO mice could not induce additional remodeling of retinogeniculate synapses. Pharmacological inactivation or knockdown with micro RNA of mGluR1 in the dLGN during the maintenance phase also caused abnormal remodeling of retinogeniculate synapses. Importantly, pharmacological activation of mGluR1 in the dLGN during late DR prevented abnormal recruitment of weak synapses and rescued the maintenance of mature connectivity in WT mice. These results demonstrate that mGluR1 is crucial for visual experience-dependent maintenance of retinogeniculate synapses.

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Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.05/B42

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: UC Berkeley, Chancellor's Fellowship

RO1 EY013528

RO1 EY019498

Title: A role for visual experience in the maturation of direction selectivity in the mammalian retina

Authors: *M. Y. EL-QUESSNY[1], M. B. FELLER[1,2]
[1]Helen Wills Neurosci. Inst., [2]Dept. of Mol. and Cell. Biol., Univ. of California, Berkeley, Berkeley, CA

Abstract: In the retina, there are synaptic and dendritic mechanisms that contribute to direction selectivity. Here, we explore how these alternative mechanisms emerge and interact in one DSGC subtype, which expresses GFP under the Hb9 promoter and prefers upward motion. Classically, DSGCs exhibit directional tuning due to asymmetric GABAergic inhibition from starburst amacrine cells. However, Hb9-GFP+ DSGCs also have asymmetric dendritic arbors that are hypothesized to contribute to the direction selective computation in these cells (Trenholm et al., 2011).
To determine how these mechanisms contribute to Hb9 DSGC direction selectivity during development, we used cell attached recordings to characterize direction selectivity in Hb9 DSGCs in the absence and presence of the $GABA_A$ receptor blocker, GABAzine. We found that GABAzine application abolishes directional tuning at the time of eye-opening, while adult Hb9 DSGCs maintain directional tuning. Voltage clamp recordings revealed that this $GABA_A$ receptor independent direction selectivity in adult mice was not dependent on asymmetric excitation, indicating that direction selectivity originated postsynaptically. To test whether visual experience influences this developmental reduction in direction selectivity's dependence on $GABA_A$ receptors, we dark-reared mice into adulthood. We found that Hb9 DSGCs in dark-reared mice did not display directional tuning in the presence of GABAzine, similar to what we see at the time of eye-opening in normally-reared animals. Moreover, we found that dark-rearing decreased the asymmetry of the dendritic morphology of Hb9 DSGCs. These results suggest that visual experience, during retinal development, plays a role in the establishment of postsynaptic contributions to direction selectivity. This model will help elucidate the role of visual experience, from the time of eye-opening to adulthood, in the maturation of retinal computations.

Disclosures: **M.Y. El-Quessny:** None. **M.B. Feller:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.06/B43

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: National Institute of Child Health and Human Development

NINDS Competitive Fellowship Award

Title: Assembly of pyramidal cell and interneuron microcircuits based on subtype identity and development lineage

Authors: ***J. C. WESTER**[1], C. J. MCBAIN[2]
[2]Lab. Cell/Molec Neurosci, [1]NIH, Bethesda, MD

Abstract: In the cerebral cortex, excitatory pyramidal cells (PCs) can be segregated based on the target of their long-range axonal projection: intratelencephalic (IT-type) PCs target cortex/striatum while pyramidal tract (PT-type) PCs target the brainstem, midbrain, and spinal cord. The output of these PCs is regulated by a diverse group of local inhibitory interneurons (INs). Importantly, INs can be also segregated into two non-overlapping subgroups based on their embryonic lineage from either the caudal or medial ganglionic eminences (CGE and MGE). Interestingly, PCs and INs are biased in their laminar distributions, such that CGE INs are primarily found in superficial layers where PT PCs are absent, while MGE INs are primarily found in deep layers where IT and PT PCs are intermingled. Here, we show that IT PCs form preferential synaptic connections with CGE INs and influence their radial migration and circuit integration during development. We used the Htr3a-GFP mouse line to target CGE INs and the Emx1-cre line to conditionally knock out the transcription factor Satb2 in PCs. Satb2 is necessary for IT-type specification and its loss results in disruption of the corpus callosum and ectopic projections to subcerebral targets. In conditional Satb2 mutants a greater percentage CGE INs were distributed in deeper cortical layers relative to controls, strongly suggesting that IT PCs instruct their radial migration. In paired whole-cell recordings in superficial layers of control mice, the dominant connection probability was from PC to CGE IN (PC to IN: 30%; IN to PC: 18%). Interestingly, in mutant mice, the PC to CGE IN connection probability was reduced (10%), while the IN to PC connection probability appeared unaffected (26%). To test whether IT PC to CGE IN connectivity is a common circuit motif, we made paired recordings in deep cortical layers, where IT and PT PCs form local overlapping microcircuits. We used retrograde tracer injections into the contralateral visual cortex or ipsilateral superior colliculus to target IT or PT PCs, respectively. Strikingly, identified IT PCs made excitatory connections onto CGE INs

at a rate of 12%, while no connections from PT PCs to CGE INs were found. To confirm this connectivity bias we used combinations of transgenic mouse lines and viral vectors to express channelrhodopsin selectively in populations of PCs of either class in deep layers. Indeed, population input from IT PCs drove robust network responses in CGE INs while input from PT PCs was rare and weak. Our data show that PC projection identity and interneuron embryonic lineage play key roles directing the assembly and organization of cortical circuits.

Disclosures: **J.C. Wester:** None. **C.J. McBain:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.07/B44

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: GSU Brains and Behavior Program fellowship

GSU Brains and Behavior Program seed grant

Title: Early TrkB signaling maintains visual receptive field refinement in adult superior colliculus by preventing a loss of inhibition

Authors: *D. B. MUDD[1], T. S. BALMER[1,2], S. L. PALLAS[1]
[1]Georgia State Univ., Atlanta, GA; [2]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: External information shapes sensory circuits during postnatal development, but plasticity is often limited in adults. Sensory deprivation can interfere with this process, sometimes leading to retention of a plastic state. Many visual response properties fail to develop under these conditions, resulting in poor vision. Surprisingly, in Syrian hamsters visual experience is not required for the refinement of receptive fields (RFs) in superior colliculus or visual cortex. Instead, early (P32-40) light exposure is necessary only for maintaining refined RFs in adulthood. The eventual expansion of refined RFs in dark-reared (DR) adults results primarily from a reduction in lateral inhibition from GABAergic interneurons in SC. We sought to identify the early, experience-driven molecular triggers that could stabilize GABAergic synapses and maintain refined RF size. Here we tested the hypothesis that, as shown for visual cortex, the neurotrophic factor BDNF and its receptor TrkB provide the link between visual experience and maturation of inhibition during a critical period (CP). To determine whether TrkB activation was sufficient to replace light exposure, Syrian hamsters were dark-reared from birth to adulthood (>P90) and given the TrkB receptor agonist 7,8 Dihydroxyflavone or vehicle during the CP for RF refinement in the superior colliculus (SC) (P33-P40). To test the necessity for TrkB activation during the CP for RF refinement, DR hamsters were exposed to light during

TrkB receptor blockade by the antagonist ANA-12. Single unit adult RF sizes in superficial SC were compared between treatment groups. TrkB activation maintained RF refinement compared to vehicle or TrkB receptor blocked, visually-stimulated animals ($p < 0.05$), suggesting that TrkB signaling pathway activation can mimic visual experience. To address mechanism, we employed immunostaining to measure levels of GAD-65, the precursor enzyme for synaptic GABA, and of the $GABA_A$ receptor α1 subunit, which is obligatory for adult $GABA_A$ receptors. TrkB receptor agonist-treated animals had higher levels of GAD-65 compared to vehicle treated or antagonist-treated animals ($p < 0.001$). No significant difference in $GABA_A$α1 receptor expression was seen between groups. Taken together, we propose that early visual activity promotes adult RF maintenance in SC via the promotion of GABAergic synapse maturation through TrkB activation. The SC and visual cortex may share a common mechanism for experience-driven plasticity of RF properties, despite differences in timing of their CPs. Modulation of TrkB signaling may facilitate investigation of pathological conditions governed by inhibitory plasticity.

Disclosures: **D.B. Mudd:** None. **T.S. Balmer:** None. **S.L. Pallas:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

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We are grateful to Prof. Goffinet for supplying the Celsr3|Dlx5/6 mouse line.

Title: How does sensory information shape early interneuron circuits to direct the maturation of the neocortex?

Authors: *J. STACEY, Z. MOLNÁR, S. J. B. BUTT
DPAG, Univ. of Oxford, Oxford, United Kingdom

Abstract: Sensory activity plays an important role in the maturation of primary visual cortex (V1), in particular, ocular dominance plasticity. Similarly, it is well established that whisker input is required for appropriate barrel development in rodent somatosensory (S1BF) cortex. These structural changes are underpinned by changes on the cortical circuit level, resulting in the unique cytoarchitecture of both cortical areas. The maturation of parvalbumin immunoreactive (PV+) interneurons (IN) is inextricably linked to the late phase of circuit development and their contribution to cortical plasticity is well documented. However, less is known about the role of

other IN subtypes during the first few postnatal weeks. Recently, we identified transient GABAergic input from L5b to L4 in neonatal S1BF of the mouse (Marques-Smith et al., 2016). This connection forms part of a reciprocal synaptic circuit between L5b somatostatin-positive (SST+) INs and L4 spiny stellate glutamatergic neurons that is only present prior to the end of the L4 critical period (~P10) in S1BF. Evidence suggests that this circuit is important for the timely acquisition of thalamic input onto L4 excitatory neurons. However, the extent to which sensory information influences remodelling of this circuit, and whether this may be a general mechanism for sensory integration remains unclear. To better understand the default network present in the absence of any sensory input we have mapped GABAergic connections onto L4 in a mouse model devoid of any thalmo-cortical/cortico-thalamic connections (Zhou et al., 2008). Intriguingly, the L5b onto L4 GABAergic connection is still present in S1BF with the time course of this transient circuit un-altered. This suggests that this connectivity emerges through a mechanism that is intrinsic to the neocortex and points towards a possible genetic component in the formation and maintenance of this early IN-spiny stellate synapse. If this circuit is genetically hardwired to appear during development and is involved in correct integration of thalamic input, we might expect it to be present in other primary sensory areas. To investigate this, we further mapped GABAergic connections in the developing V1 to determine if similar connections exist between L5 INs and L4 pyramidal cells. Using laser scanning photostimulation we found no evidence for translaminar L5 connections onto L4 neurons in V1 at early neonatal ages. This suggests that the connection between L5 SST+ INs and L4 excitatory neurons in S1BF is hardwired and area specific, highlighting a unique modality-specific role for SST+ INs in cortical development.

Disclosures: **J. Stacey:** None. **Z. Molnár:** None. **S.J.B. Butt:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: BRAIN Initiative Award U01NS094358

MSTP Training Grant T32GM007205

Title: Dual mesoscopic and two-photon imaging of neuronal activity in cortical circuits

Authors: *D. BARSON, A. S. HAMODI, G. LUR, J. A. CARDIN, M. C. CRAIR, M. J. HIGLEY
Yale Sch. of Med., New Haven, CT

Abstract: The mammalian neocortex exhibits complex spatiotemporal patterns of spontaneous and sensory-evoked activity that are necessary for the formation, refinement and function of neural circuits. Disruption of these patterns has been implicated in numerous neuropsychiatric disorders, such as autism and schizophrenia. Identifying the cellular mechanisms underlying this activity is therefore critical for understanding both normal and pathological brain development and function. Technical challenges have generally precluded establishing conceptual links between the function of networks of individual neurons and brain-wide circuit dynamics. To solve this problem, we developed a technology that allows simultaneous cellular-resolution (two-photon) calcium imaging of a local microcircuit and mesoscopic (one-photon) calcium imaging of the entire cortical surface in awake, behaving mice. Our microscope employs an orthogonal axis design whereby the mesoscopic objective is oriented downward directly above the brain and the two-photon objective is oriented horizontally, with imaging done through a glass right angle microprism implanted in the skull. We combined these imaging modalities with expression of genetically encoded calcium indicators to monitor activity of targeted subpopulations of individual neurons simultaneously with brain-wide activity. We are currently using this dual-imaging approach to directly link single neuron spiking to widespread signaling across the cortical mantle. In preliminary studies, we observed that subnetworks of neurons in layer 2/3 of both primary somatosensory and visual areas exhibit heterogeneous inter-areal correlational structure. For example, cells in these sensory areas may participate in networks linking either contralateral homotypic or ipsilateral motor regions. Additionally, we are examining how cortical functional connectivity is refined in the period after the emergence of early spontaneous activity beyond the second postnatal week in mice. Our method enables the generation of novel insights into the role of specific populations of individual neurons in the functional organization of brain circuits during healthy development and in disease, and complements other multi-scale imaging approaches to better understand brain development and clinical functional imaging data.

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Poster

116. Neural Circuit Maturation and Remodeling I

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant EY019498

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NIH Grant EY003176

Title: A role for visual experience in activity-dependent development prior to eye-opening

Authors: *A. TIRIAC[1], B. E. SMITH[2], M. B. FELLER[1,2]
[1]Mol. and Cell Biol., [2]Vision Sci., Univ. of California Berkeley, Berkeley, CA

Abstract: As early as when the eyes first open, light is known to play a critical role in the development of visual circuitry. However, whether light interacts with the developing visual system before eye-opening is not well understood. In mice, the eyelids remain closed for the first two weeks of postnatal life during which cells of the retina exhibit retinal waves, a term used to describe spontaneous correlated activity. These waves are the predominant type of neural activity before vision and have been implicated in the refinement of retinal projections to the brain. Several days before eye-opening, rod and cone photoreceptors become active components of retinal circuitry, suggesting that light-mediated responses and retinal waves could interact. Here, using two-photon imaging, we show that light modulates the frequency and area of propagation of waves, and we will present data testing the impact of light on the directionality of wave propagation. Second, we show that dark-rearing mice before eye-opening leads to reduced eye-specific segregation of axonal projections from retinal ganglion cells to the dorsal lateral geniculate nucleus. These studies will provide critical new insights on the importance of light stimulation even before eye-opening for the proper development of the visual system.

Disclosures: A. Tiriac: None. **B.E. Smith:** None. **M.B. Feller:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01MH106553

NIH Grant R21MH101663-01

Title: Immune activation produces learning deficits and alters microglia function in early juvenile development

Authors: *B. OSBORNE, J. M. SCHWARZ
Dept. of Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Immune activation during early development can have profound effects on later immune function, cognition, and behavior. Epidemiological data indicate a strong correlation between early-life immune activation and later diagnosis of disorders such as autism, schizophrenia, and depression. We have found that immune activation on postnatal day 21 (P21)

produces learning deficits in the emergence of hippocampal-dependent learning in juvenile rats at the onset of hippocampal-dependent learning in the Context Pre-exposure Facilitation Effect (CPFE) paradigm. Microglia are the resident immune cells of the brain and phagocytose cellular debris following infection or injury. Microglia are also important regulators of neuronal development. They play an active role in synapse function, plasticity, and circuit formation throughout healthy brain development. During early development, microglia are essential for the pruning and maturation of synapses which is necessary for the establishment of mature neural circuits. We hypothesize that disruptions in microglia-neuron interactions necessary for the formation of hippocampal neuronal circuits caused by immune activation on P21 underlie the learning deficits observed in the CPFE. Data on the phagocytosis of synaptic elements by microglia in the hippocampus following immune activation with lipopolysaccharide (LPS) P21 will be examined. Additionally, we will examine the expression patterns of inflammatory cytokines, genes important for microglial-neuronal signaling, and neurotrophic factors following LPS immune activation on P21.These experiments are the first to examine the impact of immune activation during an important period of hippocampal development on neuroimmune function, neural circuit formation, and cognitive development. These findings further our understanding of how immune dysregulation may precipitate subsequent and long-term mental health and cognitive disorders that originate in early development.

Disclosures: B. Osborne: None. **J.M. Schwarz:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.12/B49

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NMRC/BNIG/2043/2015

Title: Removal of perineuronal nets in visual cortices of adult murine Prmt knockout mice restores visual acuity

Authors: *M. BEGUM[1], P. M[1], K. YOKE[2], J. LI ZHUOAN[2], J. HO[3], S.-C. YEN[3], J. C. G. SNG[1]
[1]Pharmacol., Natl. Univ. of Singapore, Singapore, Singapore; [2]NUS High Sch., Singapore, Singapore; [3]Engin., Natl. Univ. Singapore, Singapore, Singapore

Abstract: Critical periods (CP) in early postnatal life are crucial for the formation of sophisticated neuronal connections for the visual system development. Our previous work demonstrated protein arginine methytransferase 8's (PRMT8), involvement in synaptic maturation and its prospect as an epigenetic modulator of developmental neuroplasticity by regulating

structural elements. We further investigate the implications of *Prmt8* knockout and their corresponding upregulation of structural proteins specifically Tenascin-R (TNR). We first validate TNR's increase in visual cortices of knockouts using real-time PCR in comparison with wild-types. TNR is known to be an essential component of perineuronal nets (PNNs) that wrap around neurons and thus consolidate neuronal circuits during development. *Prmt8* knockouts have shown hastened neuron maturation. In line with this, visual optomotor tests of adult knockout mice reveal a decrease in visual acuity. To manipulate the structural consolidation of neuronal circuitry, we performed unilateral injection of chondroitinase ABC to adult visual cortices to breakdown PNNs. Post-treatment mice show a restoration of visual acuity to wild-type levels. Although the exact mechanism is unclear at this juncture, this implies a possible reactivation of plasticity in adult mice allowing for the rescue of vision observed. We plan to further investigate this using optogenetics to probe specific classes of neurons in post-treatment mice and exploring its corresponding effects on recovery of vision.

Disclosures: M. Begum: None. **P. M:** None. **K. Yoke:** None. **J. Li Zhuoan:** None. **J. Ho:** None. **S. Yen:** None. **J.C.G. Sng:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.13/B50

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant GM076430

NINDS Grant NS050274

Title: Severe prefrontal cortex abnormalities in mice lacking ipRGC signaling

Authors: *L. LAZZERINI OSPRI[1], S. HATTAR[2]
[1]Johns Hopkins Univ., Baltimore, MD; [2]NIH, Bethesda, MD

Abstract: A new disynaptic pathway has been discovered that connects the retina to the infralimbic (IL) and prelimbic (PL) cortex via the thalamus, with its origin in intrinsically-photosensitive retinal ganglion cells (ipRGCs). It is known that a subset of this pathway's prefrontal target area, the IL cortex, contains a population of pyramidal neurons exquisitely sensitive to stress exposure. Even single minute-long applications of physical stressors are reported to cause significant morphological changes in these neurons' apical dendritic tree. Given that the retino-thalamo-cortical pathway provides a major previously-undetected input to its prefrontal target, we set out to investigate the cytoarchitecture of this target area in ipRGC-ablated mice.

Two transgenic lines were used: $Opn4^{aDTA/aDTA}$ have an attenuated diphtheria toxin A subunit inserted into the melanopsin locus, which results in the progressive degeneration of M1 ipRGCs (the subtype with the highest level of melanopsin expression) starting at 2 months of age, with complete degeneration by 6 months; $Opn4^{Cre}$;$Brn3b^{DTA}$ express diphtheria toxin in those ipRGCs that express the transcription factor Brn3b. Only ~200 ipRGCs do not express Brn3b; these cells exclusively innervate the suprachiasmatic nucleus, are sufficient for circadian photoentrainment, and are the only ones that survive in $Opn4^{Cre}$;$Brn3b^{DTA}$ animals. Notably, Brn3b is expressed nowhere in the cerebral cortex. The wild type controls were of C57BL/6 background. Only male mice were used.
The morphometric analysis was conducted on Neurolucida-reconstructed neurons from Golgi-stained brain sections. The neurons to be traced were selected according to the following criteria: 1. Placement in the infralimbic and ventral prelimbic cortex. 2. Pyramidal type. 3. Distance from the soma to the pial surface comprising layers 3 and 4. 4. Shape of the dendritic tree not suggestive of a layer 5 or short-shaft layer 2/3 neuron. 5. Apical dendritic tree mainly unfolding within the middle third of the section, well isolated, intact and not obscured by neighbors. Reconstructed neurons from 6-month-old $Opn4^{aDTA/aDTA}$ (N=14) and $Opn4^{Cre}$;$Brn3b^{DTA}$ (N=9) mice show a highly significant ($p<0.0003$) and striking ~35% retraction of their apical dendritic trees compared to wild types (N=11) (quantified by total dendritic tree length, and branch numbers). No significant differences were found in a control region (motor cortex).
We conclude that ipRGC signaling appears necessary for the cytoarchitectural integrity of this limbic cortical region involved in, inter alia, mood regulation and social behavior.

Disclosures: L. Lazzerini Ospri: None. **S. Hattar:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.14/B51

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant R01 EY027003

Title: Roles of delta-protocadherins in neural circuit assembly

Authors: *S. LIGHT, M. EMOND, J. JONTES
The Ohio State Univ., Columbus, OH

Abstract: Protocadherins (pcdhs) belong to a diverse family of cell adhesion molecules involved in a variety of developmental processes including cell migration, neurogenesis, axon growth, and dendrite arborization. Mutations in several protocadherins are associated with neurodevelopmental defects including autism spectrum disorders, schizophrenia, and epilepsy. In

particular, mutations in human *PCDH19* cause a specific form of infant-onset epilepsy. Our long-term goals are to determine the molecular and cellular mechanisms of Pcdh19 and other protocadherins, and to understand how these molecules function during neural development to produce correct brain structure and function. Our lab has previously shown that *pcdh19* is expressed in columns of neurons in the zebrafish optic tectum that originate from single neuronal progenitors. P*cdh19* mutations disrupt columnar architecture and impair visually-guided behaviors in zebrafish larvae. To explore the impact of *pcdh19* loss on neural function, we employed both *in vivo* imaging to explore how Pcdh19 guides circuit assembly and proteomics to identify intracellular pathways downstream of Pcdh19. First, we performed whole-brain calcium imaging of wild type and *pcdh19* mutant larvae over the first developmental week using *in vivo* two-photon microscopy. Mutant fish display alterations in neuronal activity patterns, which suggest that pcdh19 is essential for establishing appropriate neuronal connections in the developing brain. In ongoing work, we are investigating the effects of *pcdh19* loss on visually-evoked neural activity and susceptibility to drug-induced seizure activity. Additionally, we are characterizing changes in neuroanatomical organization of *pcdh19* mutants with immuno-histochemistry. Using proximity-dependent biotinylation and proteomics, we identified a number of intracellular binding partners for Pcdh19 that have known roles in actin assembly, receptor trafficking, cell polarity, and the Wnt and MAP kinase signaling pathways. We are currently validating some of these proteins and investigating signaling mechanisms downstream of Pcdh19. In addition, we are employing some of the same approaches to explore other protocadherins in order to better understand how this family of cell adhesion molecules guides development of the vertebrate nervous system.

Disclosures: S. Light: None. **M. Emond:** None. **J. Jontes:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.15/B52

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Howard Hughes Medical Institute (grant #55007652)

Argentine Agency for the Promotion of Science (PICT2015-3814).

Title: Development of adult-born granule cell connectivity with different interneuron networks

Authors: *A. I. GROISMAN, S. M. YANG, S. G. TEMPRANA, A. F. SCHINDER
Leloir Inst. (IIBBA-CONICET), Capital Federal, Argentina

Abstract: Adult neurogenesis provides a continuous pool of new granule cells (GCs) that participate in information processing in the dentate gyrus of the hippocampus, which is involved in memory and learning. As new GCs transition towards maturity, they reliably recruit GABAergic feedback loops that restrict spiking of neighbor GCs, a mechanism that would promote sparse coding. We studied how GCs of different ages become integrated into the pre-existing circuit of the adult mouse dentate gyrus. In particular, we chose two major population of GABAergic interneurons (INs) of the hippocampus: Parvalbumin expressing cells (PVcs) and Somatostatin expressing cells (SSTcs). We combined optogenetics and acute slice electrophysiology to activate PVcs or SSTcs and GCs at different stages of maturation and studied their connectivity in both directions, interneuron to GCs and viceversa. As a first approach, we applied overall inhibition on the granule cell layer by activating each IN type and found that the area of the population spike elicited by synchronous activation of the perforant path was reduced by 60 % and 80% when stimulating SSTcs and PVcs respectively. We also built a synaptogenesis temporal map for each IN population and observed that connectivity between PV and GCs (input and output) reached maturation when GCs were at least six weeks old. For SSTcs, the inhibitory current increased gradually with GCs development, while the GCs output connectivity developed much later (at 11 weeks old) when compared to PVcs. This approach together with previous data shows that PVcs feedback inhibition is recruited by GCs before reaching maturity, while SSTcs are only activated long after GCs have achieved full maturation.

Disclosures: A.I. Groisman: None. **S.M. Yang:** None. **S.G. Temprana:** None. **A.F. Schinder:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.16/B53

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ey021222

Title: LRRTM1 contributes to the assembly of complex retinogeniculate synapses in mouse visual thalamus

Authors: *A. MONAVARFESHANI[1,2], G. STANTON[1], J. SU[1], K. SU[1], K. SWILLING[1], M. A. FOX[1,2]
[1]Virginia Tech. Carilion Res. Inst., Roanoke, VA; [2]Biol. Sci., Virginia Tech., Blacksburg, VA

Abstract: Retinogeniculate (RG) synapses are critical for regulating the flow of visual information from retina to primary visual cortex (V1). We recently discovered that RG synapses

in the mouse dorsal lateral geniculate nucleus (dLGN) differ anatomically and physiologically from retinal synapses in all other retino-recipient nuclei. Not only are retinal terminals significantly large and functionally strong in dLGN, but they can be classified into two distinct morphologies: simple RG synapses that contain a single retinal terminal and complex RG synapses that contain numerous retinal terminals that converge onto the same region of postsynaptic dendrite. Here we sought to identify factors in dLGN that lead to the development of these unique synapses. RNAseq analysis identified Leucine-Rich Repeat Transmembrane Neuronal 1 (LRRTM1) as target-derived synaptic organizer enriched in dLGN, but not other retino-recipient nuclei, during the developmental maturation of RG synapses. To test its role in RG synapse development, we assessed the morphology of RG synapses in targeted mutant mice lacking LRRTM1 (*lrrtm1*$^{-/-}$). Anterograde labeling of retinal terminals by intraocular injection of fluorophore-conjugated Cholera Toxin B (CTB) and immunostaining for Vesicular Glutamate Transporter 2 (VGluT2) revealed smaller terminal "puncta" in dLGN in the absence of LRRTM1. These results suggest that either each retinal terminal was smaller in mutants or that complex RG synapses were absent. To answer this question we used serial block face scanning electron microscopy (SBFSEM) and brainbow multicolor labeling of retinal terminals. Ultrastructural analysis revealed a significant reduction in the number of complex RG synapses in *lrrtm1*$^{-/-}$ dLGN accompanied with an increase in the size of individual retinal terminals in dLGN of *lrrtm1*$^{-/-}$ mice. Moreover, AAV-brainbow labeling confirmed the loss of complex RG synapses in *lrrtm1*$^{-/-}$ mice. Thus, these studies identified LRRTM1 as a necessary target-derived factor that drive complex RG synaptogenesis. We are now using these mutant mice to determine the role of complex RG synapses in processing and relaying visual information from retina to primary visual cortex.

Disclosures: **A. Monavarfeshani:** None. **G. Stanton:** None. **J. Su:** None. **K. Su:** None. **K. Swilling:** None. **M.A. Fox:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.17/B54

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: the National Key Research and Development Program of China (2016YFA0100802)

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the Foundation of the Ministry of Education of China (20130071110065)

Title: Eye opening selectively modulates inhibitory synaptic transmission in the developing visual cortex

Authors: *Y.-C. YU[1], W. GUAN[2], J.-W. CAO[2], Y. FU[2]
[1]Inst. of Brain Sci., [2]Fudan Univ., Shanghai, China

Abstract: Eye opening, a natural and timed event during animal development, influences cortical circuit assembly and maturation; yet, little is known about its precise effect on inhibitory synaptic connections. Here we show that coinciding with eye opening, the strength of unitary inhibitory postsynaptic currents (uIPSCs) from somatostatin-expressing interneurons (SST-INs) to nearby excitatory neurons, but not interneurons, sharply decreases in layer 2/3 of the mouse visual cortex. This drastic change is prevented by dark rearing or binocular lid suture, and reproduced by artificial opening of sutured lids. Mechanistically, this weakening in synaptic transmission is accompanied by a significant decrease in the number of presynaptic release sites as well as a reduction in the postsynaptic quantal size mediated by the loss of alpha5-containing $GABA_A$ receptors. Together, our study reveals a selective developmental regulation in GABAergic circuits in the cortex driven by eye opening likely crucial for cortical maturation and function.

Disclosures: **Y. Yu:** None. **W. Guan:** None. **J. Cao:** None. **Y. Fu:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.18/B55

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: CIHR

Title: Refinement of presynaptic axons in the absence of synaptic activity

Authors: *Y. CHONG[1], N. SAVIUK[1], B. PIE[1], N. SONENBERG[1], P. HAGHIGHI[2], E. COOPER[1]
[1]McGill Univ., Montreal, QC, Canada; [2]Buck Inst. for Res. on Aging, Novato, CA

Abstract: During postnatal development, neuronal circuits throughout the nervous system continually refine their connections by strengthening some inputs and eliminating others. A well-

accepted hypothesis for this refinement is that it occurs through a competitive process that requires synaptic activity. Our work demonstrates that this hypothesis is incomplete: We show that in mice that lack the eukaryotic initiation factor 4E binding protein (4E-BP), a critical repressor of cap-dependent translation, synapses in sympathetic ganglia refine in the complete absence of synaptic activity.

To demonstrate that connections refine without synaptic activity, we examined the innervation of sympathetic neurons in 2 mouse lines: One with a deletion in the α3 subunit of postsynaptic nicotinic acetylcholine receptors at synapses in sympathetic ganglia; the deletion of α3 causes synapses in sympathetic ganglia to be electrophysiologically silent (α3 KO). In the other line, 4E-BP and α3 have both been deleted (α3/4E-BP DKO). In both lines, we quantified the innervation using lipophilic dye tracing, immunostaining, electrophysiology. And, we restored synaptic transmission using viral-mediated gene transfer to investigate the role for postsynaptic activity.

In WT mice, sympathetic neurons formed elaborate dendritic arbors, and preganglionic axons targeted their synapses to the dendritic domain. In contrast, sympathetic neurons in α3 KO mice showed stunted dendritic growth, and axons targeted silent synapses to the cell soma. At birth, sympathetic neurons in both WT and α3 KO mice were hyperinnervated by ~8 preganglionic axons. Over the first postnatal month, neurons in WT mice refined their innervation to ~3 inputs, while those in α3 KO mice remained hyperinnervated and axons did not refine unless synaptic activity was restored. In addition, sympathetic neurons in α3 KO mice showed reduced levels of phosphorylated-4E-BP when compared to WT neurons, suggesting that 4E-BP might play a role in the activity-dependent regulation of preganglionic axon refinement. In support of this idea, when 4E-BP was deleted (α3/4E-BP DKO), preganglionic innervation to sympathetic neurons refined to ~3 inputs, even though synaptic activity was absent.

Our results demonstrate that synapses can refine in the absence of synaptic activity and identify 4E-BP as a critical player in this process. We suggest that synaptic activity engages a 4E-BP-dependent pathway that enables a retrograde signaling mechanism to coordinate the refinement of presynaptic innervation.

Disclosures: **Y. Chong:** None. **N. Saviuk:** None. **B. Pie:** None. **N. Sonenberg:** None. **P. Haghighi:** None. **E. Cooper:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

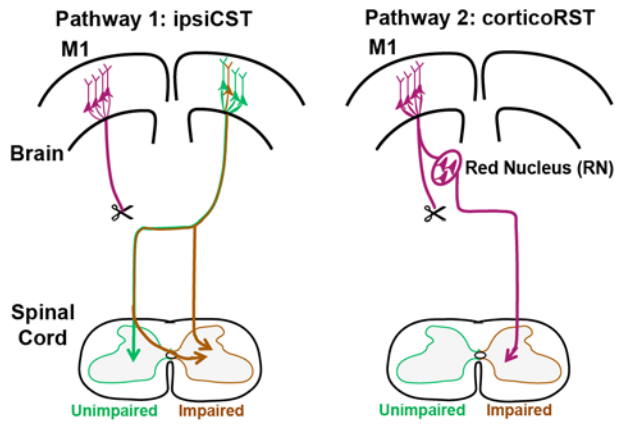
Support: NIH Grant K08NS073796

Thomas and Agnes Carvel Foundation

Title: Rats with neonatal corticospinal injury exhibit motor control from both hemispheres but anatomical plasticity only from the uninjured hemisphere

Authors: *S. LALL, T. WEN, C. PAGNOTTA, S. RATNADURAI GIRIDHARAN, J. B. CARMEL
Burke Med. Res. Inst., White Plains, NY

Abstract: * Injury to the developing corticospinal tract (CST) triggers the persistence or remodeling of spared descending motor circuits. After neonatal CST lesion, spared pathways from either cerebral hemisphere can provide motor control to the impaired forelimb. We hypothesized (Figure) that connections and control arose from the ipsiCST pathway from the uninjured hemisphere rather than by the corticoRST pathway, a bypass circuit through the brain stem, from the injured hemisphere. We cut the CST at the pyramid in postnatal day 7 Sprague Dawley rats, equivalent to full term human newborns. After the rats reached maturity, we tested skilled forelimb function—food manipulation and locomotion. To determine which hemisphere controlled the affected forelimb, we inactivated the motor cortex (M1) in each hemisphere and tested performance on a reach and turn task. Anatomical connections were assessed by injecting biotinylated dextran amine (BDA) into the motor cortex and counting labeled axons in the brain stem and spinal cord. Additionally, Fast Blue was injected into the spinal cord to count labeled neurons in the brain stem. Rats with neonatal CST injury showed persistent motor deficits in maturity. Uninjured rats exhibited forelimb deficits only after inactivation of the contralateral motor cortex, whereas rats with neonatal CST injury exhibited deficits after inactivation of each motor cortex. In contrast, increased CST and corticobulbar connections were observed only from the uninjured hemisphere. Thus, the injured hemisphere still participates in control, even though its descending motor connections do not exhibit plasticity.



Disclosures: **S. Lall:** None. **T. Wen:** None. **C. Pagnotta:** None. **S. Ratnadurai Giridharan:** None. **J.B. Carmel:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

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Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Grant-in-Aid for JSPS Fellows 15J03643

KAKENHI 16H06459

KAKENHI 16K14559

KAKENHI 15H01454

KAKENHI 15H04263

KAKENHI 22115009

Title: Three-day-long *In vivo* imaging of dendritic reorganization in barrel cortex layer 4 in neonates

Authors: *S. NAKAZAWA[1,2], H. MIZUNO[1,2], T. IWASATO[1,2]
[1]Natl. Inst. of Genet., Mishima, Shizuoka, Japan; [2]Dept. of Genet., SOKENDAI (The Grad. Univ. for Advanced Studies), Mishima, Shizuoka, Japan

Abstract: The proper cortical processing of sensory information relies on precise dendrite projection pattern of layer 4 (L4) excitatory neurons. However, processes of L4 neuron dendrite specification, which occurs during early postnatal development, are mostly unexplored. We here addressed these questions by a novel approach, long-term in vivo imaging of the neonatal mouse barrel cortex. In the mature mouse barrel cortex, spiny stellate (SS) neurons and thalamocortical (TC) axon termini form "barrels" that are morphologically and functionally distinct modules corresponding to individual whiskers on the face. In each barrel, SS neurons are located around the barrel edge and extend the basal dendrites selectively toward the barrel center, where they make synapses with specific TC axons. We visualized dendritic morphologies of individual L4 neurons in vivo using in utero electroporation-based Supernova labeling (Mizuno et al., 2014; Luo et al., 2016). Barrel arrangement was visualized by using the TC axon-GFP Tg mouse (Mizuno et al., 2014). We performed time-lapse imaging of L4 neurons for 3 days starting at postnatal day 3 (P3). We found that at P3 most L4 neurons had a long apical dendrite and simple basal dendrites. As animals grew, majority of L4 neurons lost the apical dendrite by gradual retraction. We identified these apical dendrite-losing neurons as SS neurons. In fact, at P6 most of these neurons had basal dendrites oriented toward the barrel center, which is the unique feature of SS neurons in the barrel cortex. In the meeting, based on the analyses of our in vivo

imaging data, we will discuss the mechanisms of SS neuron differentiation and dendrite reorganization in neonatal period.

Disclosures: S. Nakazawa: None. **H. Mizuno:** None. **T. Iwasato:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.21/B58

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIH/NIDCD R01 DC007695-08

Title: Single cell RNA-sequencing of a developing neural system

Authors: *A. BRANDEBURA[1], D. KOLSON[1], P. STOILOV[2], P. MATHERS[2], G. SPIROU[1]
[1]Neurosci., [2]Biochem. and Mol. Biol., West Virginia Univ., Morgantown, WV

Abstract: The calyx of Held (CH) is the largest nerve terminal in the mammalian central nervous system and the large size of this terminal, rapid period of growth (24-72 hours) and well-defined endpoint of monoinnervation onto the postsynaptic principal neurons in the medial nucleus of the trapezoid body (MNTB) make this brain region a useful model system to study the molecular mechanisms of neural circuit formation. We employed single cell RNA-sequencing (scRNA-Seq) to reveal the dynamics of gene expression among the various neuronal and nonneuronal cell types in this developing neural circuit. These high-resolution gene expression data can be used to connect signaling pathways in different cell types to structural changes in the system. Microdissections of MNTB are performed at postnatal day (P)3 during the height of CH growth. Single cell suspensions were loaded into the Fluidigm C1 Integrated Fluidic Circuit chip for single cell capture and processing for scRNA-Seq. Over 300 single cells were captured and analyzed. Most cell libraries had greater than 70% genome alignment using HiSat2. The number of detected genes was saturated at read depth of 2.5 million mapped reads per cell. We detected 5,000 to 6000 genes in most of the single cell libraries that met or exceeded this read depth threshold. Analysis of the P3 sequencing data using the R Bioconductor package yielded the identification of genes that are highly variable in expression level between different cell types. These highly variable genes were then used to cluster cells into distinct groups and subgroups. The identification of neurons in the clustering analysis was confirmed with the *En1*-Cre crossed to the *Rosa26*-tdTomato reporter. At least two distinct subtypes of astrocytes and neurons were identified and oligodendrocytes fell into distinct groups which reflected differences along a maturational spectrum. The key cellular contributors of transcripts encoding for extracellular secreted proteins, such as those involved in perineuronal net formation, were identified based on enrichment analysis. In conclusion, the single cell capture approach allows for the construction

of a transcriptional database for all major cell types in the early postnatal MNTB and this database ties gene function to structural dynamics of a developing neural circuit.

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Poster

116. Neural Circuit Maturation and Remodeling I

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.22/B59

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: NIMH 1P50MH094271

Blavatnik Accelerator Fund

NIH R01 GM093627

Title: Impaired perineuronal nets in neprilysin- and Chst15-deficient mice

Authors: *H. BAE[1], G. G. MILLER[2], H. HUANG[2], L. C. HSIEH-WILSON[2], T. K. HENSCH[1]
[1]Harvard Univ., Cambridge, MA; [2]Chem. and Chemical Engineering, Caltech, Pasadena, CA

Abstract: Parvalbumin (PV+) neurons are closely associated with a specialized extracellular matrix, called perineuronal nets (PNNs). Tighter wrapping of PNNs around PV+ neurons coincides with the time course of a critical period for visual acuity in primary visual cortex (V1), and enzymatic degradation of PNNs reopens critical period plasticity in adults. PNN formation reflects a dynamic balance of net component assembly / disassembly. Here, we examined the roles of two such regulatory proteins on postnatal V1 development. Neprilysin is a metalloproteinase located on the PV+ cell membrane, and GalNAc4S-6ST (synthesized by the *Chst15* gene) is a carbohydrate sulfotransferase that synthesizes the key chondroitin sulfate E (CS-E) sugar chain in the PNN. We find that knockout (KO) mice lacking these proteins exhibit layer-specific impairments in PNN development. Neprilysin KO mice showed reduced PNN-related gene expression early in life, had fewer WFA+ or PV+ cells specifically in L4, and displayed a 10-day delay in the maturation of visual acuity. Instead, adult *Chst15* KO mice had fewer PNN+ neurons in deep layers (L5/6) and displayed decreased PNN complexity. We confirmed the loss of CS-E by HPLC disaccharide analysis of the visual cortex in *Chst15* KO mice at P0, 7, 14, 28 and 60, but did not observe dramatic effects yet on the PNNs at P28. This suggests a gradual contribution of CS-E to PNN assembly, consistent with its high affinity for factors that regulate PV+ circuit maturation and maintenance, like Otx2. Thus, proteolytic activity by neprilysin may dynamically remodel the PNN early in their development, promoting maturation of PV neurons and subsequent visual acuity. In the absence of high affinity CS-E

binding sites, Otx2 may accumulate ectopically, as in Otx2-AA point mutant mice (Lee *et al.*, 2017), which in turn would impair PNN integrity. This suggests a potentially extended critical period plasticity in *Chst15* KO mice.

Disclosures: H. Bae: None. **G.G. Miller:** None. **H. Huang:** None. **L.C. Hsieh-Wilson:** None. **T.K. Hensch:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.23/B60

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Horizon 2020 MSCA-IF-2014 :660795

European Research Council under the European Union's FP7

Title: *In vivo* imaging of GABAergic microcircuits during postnatal development

Authors: *L. MODOL VIDAL[1], Y. BOLLMANN[1], V. VILLETTE[2], S. REICHINNECK[3], T. TRESSARD[1], A. BAUDE[1], R. COSSART[1]
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Abstract: The onset of network activity in a developing brain is characterized by the acquisition of spontaneous oscillatory coordinated activity between large numbers of maturing neurons. Such coordinated neuronal patterns play a pivotal role in the structural organization of immature and mature neuronal circuits. It is a characteristic of most developing neural systems as they have been observed in a wide array of peripheral and central tissues. Hence, to understand how neural circuits form in the normal and pathological brain, it is essential to study the underlying mechanisms of synchronization in maturing cortical networks. In the murine hippocampus and neocortex, functional maturation of interneurons has been described to be a hallmark of cortical dynamics, shaping plasticity and synaptic wiring during the course of pre- and -postnatal development. Correlated activity has been shown to be driven by GABAergic transmission *in vitro.* As well, a subset of early born GABAergic interneurons (operational *"hub"* cells) have been described to orchestrate network synchronization of hippocampal and cortical development. Although, it is evident that interneurons are important contributors to circuit formation, the *in vivo* role of GABAergic networks in early cortical dynamics is poorly understood. In the present study, we used GABAergic-specific GCaMP6s expression in the barrel cortex, together with functional multi-neuron calcium imaging *in vivo* and electrophysiology and followed maturation

of GABAergic networks during the 2 first postnatal weeks of mouse life, to understand the contribution of interneurons in the maturation of cortical networks.

Disclosures: L. Modol Vidal: None. **Y. Bollmann:** None. **V. Villette:** None. **S. reichinneck:** None. **T. Tressard:** None. **A. Baude:** None. **R. Cossart:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.24/B61

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Research Grant-Epilepsy Foundation

Title: Brain-derived neurotrophic factor (BDNF)-TrkB signaling in cortistatin interneurons is crucial for the maintenance of excitatory-inhibitory balance

Authors: *K. MARTINOWICH[1], Y. MAI[4], J. L. HILL[1], D. V. JIMENEZ[5], H. L. HALLOCK[4], M. REN[6], K. R. MAYNARD[7], H.-Y. CHEN[2], N. HARDY[8], B. J. MAHER[1], R. SCHLOESSER[9], F. YANG[3], *K. MARTINOWICH[1]
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Abstract: Cortistatin (CST) is a secreted neuropeptide that is structurally similar to somatostatin (SST)-it signals through similar receptors, but has distinct biological effects. Cortistatin gene expression (*Cort*) is restricted to a relatively small set of inhibitory interneurons in the cortex and hippocampus. Unlike SST, CST administration enhances the hyperpolarization-triggered cation current (I_h). CST is implicated in regulation of slow-wave activity (SWA) during sleep, and also has anti-convulsant properties. To better understand the function of CST-expressing interneurons in brain function, we crossed transgenic mice expressing Cre-recombinase under the control of the *Cort* promoter (CST^{Cre}) to mice with a floxed attenuated diphtheria toxin allele to selectively ablate CST-positive interneurons. We observed that these mice develop spontaneous seizures and premature death by postnatal day 23 (P23), indicating that CST expressing cells are important for maintaining excitatory-inhibitory balance (E-I). *Cort* expression peaks during the second week of postnatal development, coinciding with a sharp developmental increase in brain-derived neurotrophic factor (BDNF) levels. *Cort* expression is strongly correlated with BDNF signaling, which plays a crucial role in development of cortical inhibition. We thus hypothesized that BDNF signaling via tropomyosin receptor kinase B (TrkB) is important for CST-positive

interneurons to maintain E-I balance. To test this hypothesis we crossed CST^{Cre} mice to mice with a floxed TrkB allele ($TrkB^{flox/flox}$) to selectively delete TrkB from CST-positive interneurons. We observed spontaneous seizures starting at P21. Seizures were visually scored using a modified Racine scale and monitored by video-electroencephalography (EEG). $CST^{cre}/TrkB^{flox/flox}$ mice mice had increased baseline EEG amplitudes and increased power in the 25-40 Hz range during identified seizure epochs. Next, we crossed $CST^{Cre}/TrkB^{flox/flox}$ mice to floxed TdTomato reporter (tdTom) mice to assess if TrkB deletion impacted cell migration, survival or physiology. Numbers and laminar distributions of tdTom-positive cells in cortex and hippocampus were unchanged suggesting that loss of TrkB did not affect cell migration or survival. Finally, ex vivo slice recordings in $CST^{cre}/TrkB^{flox/flox}$ mice revealed a selective deficit in the frequency of spontaneous ePSCs in CST interneurons with TrkB deletion, suggesting that loss of BDNF-TrkB signaling affects CST cell excitability. In summary, these data demonstrate that BDNF signaling via TrkB in CST-positive interneurons is crucial for maintaining E-I balance.

Disclosures: **Y. Mai:** None. **J.L. Hill:** None. **D.V. Jimenez:** None. **H.L. Hallock:** None. **M. Ren:** None. **K.R. Maynard:** None. **H. Chen:** None. **N. Hardy:** None. **B.J. Maher:** None. **R. Schloesser:** None. **F. Yang:** None. **K. Martinowich:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.25/B62

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: Scottish Rite Charitable Foundation

Title: The clustered Protocadherins promote the wiring and survival of inhibitory interneurons (in the developing brain)

Authors: *C. H. CARRIERE[1], J. L. LEFEBVRE[1,2]
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Abstract: The clustered Protocadherins (Pcdh) comprise ~60 cadherin-related proteins with an extraordinary potential for cell-surface diversity and wiring specificity in the nervous system. The Pcdhs are encoded by the three tandemly-arrayed gene clusters, *Pcdh-alpha* (α), *-beta* (β), and *-gamma* (γ). Pcdh isoforms have been shown to be combinatorially expressed among single neurons and to engage in homophilic interactions. With properties that amplify the diversity and selectivity of cell-surface interactions, Pcdhs could serve as a recognition code to mediate complex patterns of connectivity. Genetic studies of mice lacking Pcdh clusters have revealed

diverse roles in dendrite and axonal arborization, synaptic development, and neuronal survival. We have previously shown that the γ-Pcdhs are essential for dendrite self-avoidance and interneuron survival in retinal circuit assembly. In retina and spinal cord, Pcdhs promote the survival of interneurons during the period of developmental cell death but whether these roles extend to developing neurons in the brain remains unknown. Here we provide evidence that γ-Pcdhs are essential for the development and survival of inhibitory interneurons in multiple brain regions. Juvenile mice lacking γ-Pcdhs among GABAergic neurons exhibit decreased body weights and a robust clasping phenotype that begins at postnatal day 14. γ-Pcdh mutant animals also demonstrate significant deficits in motor function, increased anxiety-related behaviours, and spontaneous seizures. We recorded baseline electroencephalogram (EEG) activities in the cortex, and found seizure activities, which was accompanied by spasm behaviours. To determine what roles γ-Pcdhs play at the cellular level, we employed unbiased stereological procedures to calculate the volumes and to quantify cell counts in multiple regions, such as the somatosensory cortex, globus pallidus, and hippocampus. Volumes of all three regions were significantly reduced in juvenile mice lacking γ-Pcdhs, which was confirmed by magnetic resonance imaging (MRI). We also show significant reductions in the numbers of parvalbumin-positive inhibitory interneurons. We will present ongoing studies to determine how γ-Pcdhs mediate local interactions to regulate the survival and distribution of other inhibitory interneurons within the neocortex, and the synaptic connectivity onto target cells. Our results support a role for Pcdhs in the development of inhibitory interneurons in the cortex and other brain regions. These studies could yield new insights on the cell interactions that specify interneuron integration and establish the inhibitory circuitry in the developing brain.

Disclosures: C.H. Carriere: None. **J.L. Lefebvre:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.26/B63

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ALW Open Program 822.02.006

NWO Vici 865.12.001

Title: Cholinergic modulation of spontaneous activity in the mouse neonatal cortex

Authors: *G. HOUWEN, N. ZABOURI, C. LOHMANN
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Abstract: In an adult mouse, cholinergic modulation of activity in the visual cortex is involved in reward mediated learning and attention. These functions require input from the retina. In the neonatal mouse, visual information is hardly available. The retina becomes light sensitive around postnatal day (P) 10, and eye opening occurs at P14. Somewhat counterintuitively, cholinergic fibers from the basal forebrain innervate the primary visual cortex (V1) as early as P4. Between that age and eye opening, cortical activity is spontaneous activity, which is required for the refinement of connections in the brain. Here, we asked whether the early cholinergic innervation of the cortex regulates spontaneous activity in the developing cortex.
Spontaneous activity occurs in bursts. To measure these bursts in anesthetized mice *in vivo*, we used 2-photon imaging of layer II/III cells filled with the calcium indicator OGB-1. Typically, 30-60 cells were imaged simultaneously. Since acetylcholine is known to decrease correlations between neurons in an adult, we measured co-activity within the bursts. After recording baseline co-activity levels, atropine, a muscarinic antagonist, was applied on top of the cortex. We found that it significantly increased co-activity, suggesting that the effect of acetylcholine in neonates and adults is similar.
Since it has been shown that acetylcholine reduces the spread of activity in the cortex, we hypothesized that this would also hold true for the developing cortex. To address this question, we used *in utero* electroporation to express GCaMP6s in layer II/III of the cortex. We used *in vivo*, awake, large field calcium recordings to measure activity in V1, the primary somatosensory cortex (S1) and the higher order areas in between. After application of atropine on the cortex, events in V1 were commonly activating V1 entirely, and events in the barrel cortex were more frequently affecting a single barrel. In two higher order visual areas, the rostrolateral area (RL) and the anterolateral area (AL), activity was diminished. This suggests that acetylcholine is actively reducing the spread of spontaneous activity within primary sensory areas, and promoting activity in higher order areas. Therefore, we hypothesize that acetylcholine is required for the refinement of the connection between primary and higher order sensory cortices. Moreover, the evidence presented here shows that the neonatal cholinergic innervation of the cortex regulates spontaneous activity similarly as in adults.

Disclosures: G. Houwen: None. **N. Zabouri:** None. **C. Lohmann:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.27/B64

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: From emitted to elicited neuronal activity in the neonatal piriform cortex

Authors: E. ORURO[1], G. PARDO[2], I. ESPÍNDULA[2], *M. E. CALCAGNOTTO[3], M. IDIART[1]
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Abstract: Introduction: Behavior studies have shown that infant rats remain exclusively in the nest during the first postnatal week. In this environment, the occurrence of certain behaviors of pup, coincident with the maternal presence inside the nest and followed by maternal sensorial stimulation, are more likely to occur in future events when the mother is inside the nest. We hypothesize that in the early days of postnatal life, the mother's odor hardly elicits the pup's behaviors in the nest. At PND 6 the mother stays longer outside the nest than at PND 2. These longer periods outside, could facilitate the appearance of the first behaviors elicited by the mother's odor. **Methods:** In order to test this hypothesis we use an artificial circuit of the initial olfactory system and compute the effects of different stimuli, the odor of the nest, the odor of the mother and the contact of the mother. These stimuli were presented in a temporal sequence, according to experimental data of maternal behavior reported for the PND 2, 4 and 6. Randomly, 3 groups of five neurons of the piriform cortex were selected to represent the projections of the frontal cortex. One of the groups of these neurons was activated during the presence of the mother's odor and at the beginning of maternal contact at all three ages; the other two groups were not activated. As control of the computational circuit, another experiment was simulated for PND 2, 4 and 6 and 3 groups of five neurons of the piriform cortex were randomly selected. Two groups of these neurons were indifferently activated during the presence of mother odor, nest odor and maternal contact, and the other group was not activated. Finally, we simulated the mother entering to the nest and analyzed the spontaneous firing rate of the selected neurons. **Results:** For control experiment, the presence of the mother's odor at PND 2, 4 and 6 did elicited spontaneous firing different similar to no activated neurons. In the activated neurons in coincidence with the presence of the mother's odor, we found that the mother odor at PND 2 and 4 also elicited spontaneous firing similar to no activated neurons. At PND 6 the activated neurons showed higher spontaneous firing rate when compared with no activated neurons. **Conclusions:** Our results indicated that the maternal stays longer outside the nest may allow the emitted neural activity in coincidence with the mother's odor to become the elicited activity for the mother's approach to the nest.

Disclosures: E. Oruro: None. **G. Pardo:** None. **I. Espíndula:** None. **M.E. Calcagnotto:** None. **M. Idiart:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.28/DP01/B65 (Dynamic Poster)

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ERC Consolidator Grant Neuropioneers

Title: Whole brain distribution of fate mapped glutamatergic neurons

Authors: *Y. BOLLMANN[1], L. CAGNACCI[2], R. COSSART[2], A. BAUDE[3]
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Abstract: Cortical glutamatergic neurons are generated throughout an extendedembryonic period. Recent studies, including from our lab [Marissal et al.Nat. Commun. (2013)], indicate that the glutamatergic cells that originatefrom the earliest stages of neurogenesis are critically involved incoordinating neuronal activity (Marissal et al 2013) as well as ininstructing the maturation throughout large cortical areas [Donato et al.Science (2017)]. Moreover, neurons born at similar time points are morelikely to be interconnected [Deguchi et al. Nat. Neuroscience (2011)]. Inthis study, we present a first step towards characterizing the whole brainconnectome of glutamatergic neurons (GNs) labeled according to theirdate of birth. We take a population approach by describing the distribution(quantification) of GNs in the whole brain to create an Atlas using lightsheetmicroscopy on clarified whole brains (CUBIC). We also quantify thesomatic GABAergic innervation of GNs according to their date of birth.To label GNs born at different times of embryogenesis, we apply a geneticfate mapping approach using a tamoxifen-dependent Cre-inducibletransgenic mouse model (Ngn2CreERwt/-/ RCE-LoxP+/+ -Tdtomato, AI14).In order to label GNs at different times of gestation, tamoxifen was givenat embryonic days 12.5 (E12.5), E14.5 and E16.5.

Disclosures: Y. Bollmann: None. **L. Cagnacci:** None. **R. Cossart:** None. **A. Baude:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.29/C1

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Support: ERC Consolidator Grant NeuroPioneers

French government MENRT grant

Title: Structure and function of early born GABA neurons in the CA1 region of the hippocampus

Authors: *C. GOUNY[1], D. ANGULO-GARCIA[1,2,3], T. TOULAT[1], A. BAUDE[1], R. COSSART[1]

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Abstract: During early postnatal development, cortical neuronal networks produce successive forms of spontaneous coordinated neuronal activity that provide key signals for circuit maturation (Crépel et al. 2007 - Allene et al. 2008, 2012). Here we focus on Giant Depolarizing Potentials (GDPs), a synapse-driven synchronization (Ben Ari et al. 1989). It was previously shown that the developing hippocampal CA3 network followed a scale-free functional topology involving GABA neurons acting as "hubs". Moreover, perturbation of a single functional GABA hub had an impact on the occurrence (acceleration or deceleration) of GDPs, thus demonstrating that these were also "operational hubs" (Bonifazi et al. 2009; Cossart et al. 2014). Using genetic fate mapping, early born GABA neurons (EbGABA) were shown to act as operational hubs in the CA3 region (Picardo et al. 2011). Here we focus on the CA1 region of the hippocampus, which is structurally and functionally different from CA3. Using calcium imaging and targeted whole cell recordings, we show that stimulation of CA1 EbGABA neurons impacts GDPs in two different ways. First, stimulation affects the rate of GDP occurrence. Secondly, we identify "driver cells", i.e. neurons whose effect upon stimulation is to lock the timing of GDPs to the stimulation. In addition, these EbGABA neurons in CA1 display an exceptionally widespread axonal arborization, which may bear their function. The present results support the idea that EbGABA, throughout all regions of the developing hippocampus, are key elements in shaping early network dynamics.

Disclosures: C. Gouny: None. **D. Angulo-Garcia:** None. **T. Toulat:** None. **A. Baude:** None. **R. Cossart:** None.

Poster

116. Neural Circuit Maturation and Remodeling I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 116.30/C2

Topic: A.06. Synaptogenesis and Activity-Dependent Development

Title: Computational simulation of the maternal odor on neonatal learning in the nest

Authors: *G. PARDO, I. ESPÍNDULA, E. ORURO
UFRGS, Porto Alegre, Brazil

Abstract: Introduction: Studies have shown that neonatal rats exhibit high ability to learn artificial odor associated with stimulus that mimics maternal care. It is presumed that this association also occurs under natural circumstances within the nest. During the first 6 postnatal days (PND), maternal care shows variation with a progressive increase in maternal absence of the nest. We hypothesized that the maternal care profile at PND 6 could shape the olfactory

neural circuit to distinguish the mother´s odor from the nest´s odor better than the profile at PND 2. Methods:To test our hypothesis, we applied a maternal conditioning regime in PND 2, 4 and 6 pups, using a computational model of the olfactory system. We simulated the norepinephrine release (from Locus Coeruleus) as the unconditioned stimulus (US); and the mother´s and the nest´s odor as conditioned stimulus (CS). Both CS were presented differently in order to represent the profile of the mother inside and outside the nest, based on experimental data. We quantified the firing rate of pyramidal neurons of the piriform cortex in response to US and CS. After conditioning, we simulate the pup within the nest exposed to nest´s odor (first step). Then, we simulate the proximity of the mother to the nest through her odor (second step). Results: We found that the firing rate did not change at PND 2, 4 and 6 in the first step. The three ages show an increase at the beginning of the first step and a decrease at the end. This decrease continues during the beginning of the second step. However, the firing rate at PND 2 continues to decrease to the end of the second step, at PND 4 it become stable and at PND 6 it increases.Conclusions: These results suggest that the profile of maternal care at PND 6, outside and inside the nest, allows a greater distinction of the mother´s odor and the nest´s odor than at PND 2.

Disclosures: G. Pardo: None. **I. Espíndula:** None. **E. Oruro:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 117.01/C3

Topic: A.07. Developmental Disorders

Support: National Institute on Alcohol Abuse and Alcoholism (NIAAA P50AA017823) to the Developmental Exposure Alcohol Research Center (DEARC)

Title: Ethanol exposure disrupts the growth of the cortical dendrite and aberrantly activates Src-family kinases

Authors: *D. WANG[1,2], J. ENCK[1,2], B. W. HOWELL[1], E. C. OLSON[1,2]
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Abstract: Ethanol exposure during pregnancy can result in deleterious effects on fetal brain development and subsequent postnatal cognitive development. However, the multiple cellular and molecular mechanisms underlying these deficits have not been well established. We have previously shown that 4 hr ethanol exposure disrupted dendritic morphology in developing deep layer cortical neurons. Here, we imaged developing dendrites in embryonic cortical explants to determine the time-course of ethanol-induced dendritic destabilization. Multiphoton microscopy was performed on embryonic mouse whole hemisphere explants two days after labeling by

electroporation with a pCAG-tdTomato construct on E13. We have previously shown that the nascent dendrite emerges by direct transformation of the leading process of the migrating neuron. During this terminal phase of neuronal migration the dendritic arbor increases ~2.5-fold in size and branching in a 120 minute period. In contrast, ethanol-exposed neurons showed a rapid (<10 minute) destabilization and partial collapse of the nascent dendrites. Interestingly, ethanol exposure did not prevent somal translocation suggesting the terminal period of neuronal migration may be largely unaffected by acute ethanol exposure. A similar dendritic destabilization was previously observed in the Reelin-deficient (*reeler*) mouse cortex. Therefore, we examined whether ethanol exposure prevented Reelin from activation of Src-family kinases and phosphorylation of the adaptor protein Dab1 in primary cortical cultures. Surprisingly ethanol by itself caused a rapid (10 minute) increase in phosphorylated tyrosine content which was blockable by PP2, a selective inhibitor of Src family kinases (SFKs). However, in contrast to Reelin alone, ethanol exposure increased tyrosine phosphorylation on multiple proteins, not just Dab1. Increased phosphotyrosine immunoreactivity was observed in some but not all cultured neurons that were also immunopositive for the immature neuronal marker Dcx. These results raise the possibility that aberrant SFK activation in a subset of immature cortical neurons may contribute to the ethanol-induced disruption of dendritic development.

Disclosures: **D. Wang:** None. **J. Enck:** None. **B.W. Howell:** None. **E.C. Olson:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 117.02/C4

Topic: A.07. Developmental Disorders

Support: the Ministry of Education, Culture, Sports, Science and Technology, Japan (grant no. 16K01954)

the Promotion and Mutual Aid Cooperation for Private Schools of Japan

Title: HPC-1/syntaxin1A regulates reciprocal feedforward interactions between DA and OXT systems, which, in turn, affect social behavior

Authors: *T. FUJIWARA[1], ***T. FUJIWARA**[1], T. KOFUJI[1,2], T. MISHIMA[1], Y. TERAO[1], K. AKAGAWA[1]
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Abstract: HPC-1/syntaxin1A (STX1A) is known as a neuronal SNARE protein which regulates vesicle exocytosis. Recent human genetic studies revealed that the *STX1A* gene was associated with neuropsychological features in patients with autism spectrum disorder (Kofuji et al 2017).

Patients with this disorder commonly show atypical social behavior. It was reported that OXT recovered these behavioral abnormality (Transl Psychiatry 2016). We previously reported that *STX1A* gene knockout mice (STX1A KO) showed reduction of monoamine and neuropeptides release (Fujiwara et al 2010, Mishima et al 2012), but glutamatergic and GABAergic fast synaptic transmission was almost normal. We also reported that STX1A KO exhibited unusual social behavioral, which resembles the abnormal social behavior observed in oxytocin (OXT) or OXT receptor knockout mice. Interestingly, the unusual social behavior in STX1A KO was rescued by OXT (Fujiwara et al 2016).
Here, we analyzed social behavioral profiles in STX1A KO in detail with useful method for evaluating social behavior and studied the mechanism underlying the unusual social behavior. Pharmacological studies revealed that unusual social behavior in STX1A KO was ameliorated by administration of D1 receptor agonist or OXT. Interestingly, the effect of D1 receptor agonist was suppressed by OXT receptor antagonist and the effect of OXT was suppressed by D1 receptor antagonist. We also analyzed OXT and DA release in STX1A KO. We found that DA-induced OXT release was suppressed and OXT-induced DA release was suppressed in STX1A KO. These results suggest that neurotransmission using STX1A regulates reciprocal feedforward interactions between DA and OXT systems, which, in turn, affect social behavior.

Disclosures: **T. Fujiwara:** None. **T. Kofuji:** None. **T. Mishima:** None. **Y. Terao:** None. **K. Akagawa:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 117.03/C5

Topic: A.07. Developmental Disorders

Support: the Ministry of Education,Culture, Sports, Science and Technology (no. 24300142)

the Promotion and Mutual Aid Corporation for Private Schools of Japan

Title: Disturbance of HPC-1/syntaxin1A gene expression and variation of its gene number are highly associated with autism spectrum disorder

Authors: ***T. KOFUJI**[1,2], T. FUJIWARA[2], T. MISHIMA[2], Y. HAYASHI[3], M. TAMARU[4], Y. TERAO[2], K. AKAGAWA[2]
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Abstract: It is thought that the pathogenesis of human neuropsychiatric disordes is associated with synaptic dysfunction. HPC-1/syntaxin1A (STX1A) is one of neuronal SNARE proteins which regulates vesicle exocytosis at pre-synaptic terminals, and contributes to neural functions in central nervous system by influencing to synaptic transmission. Recently, it was reported that STX1A gene possibly related to human neuropsychiatric disorders such as attention-dificit/hyperactivity disorder (ADHD) and asperger syndrome. In this study, we examined if STX1A gene expression was correlated with autism spectrum disorder (ASD) by real time quantitative RT-PCR using ASD patients samples. We found that some ASD patients had haloidy for STX1A gene (6.0%), and STX1A mRNA expression was reduced in these cases. STX1A gene haploidy was not observed in the parents and siblings of ASD patients with STX1A gene haploidy. Furthermore, there was a wide variation of STX1A mRNA expression in ASD patients compared to control group, however, mean STX1A mRNA amount in ASD patients was higher than that of control group using blood samples. These observations suggest that STX1A gene expression may be disturbed in a part of ASD. To further study if disturbance of STX1A gene expression causes neuropsychiatric abnormalities, the behavioral profiles in STX1A gene ablated mice (null and heterozygote mutants) were analyzed. STX1A gene ablated mice exhibited unusual behavioral profiles in learning and memory ability, selective attention and social behavior (communication ability). These abnormal behavioral profiles resemble symptoms of human ASD patients. Furthermore, those abnormal profiles in STX1A null mutant mice were worse than those in STX1A heterozygote mutant mice, indicating that reduction of STX1A gene number enhanced unusual profiles of mutant mice. In addition, these abnormal behavioral profiles in STX1A gene ablated mice were caused by reduction in secretion of serotonin or oxytocin as observed in human ASD patients. Considering these results, the disturbance of STX1A gene expression and variation of its gene number are highly associated with ASD.

Disclosures: T. Kofuji: None. **T. Fujiwara:** None. **T. Mishima:** None. **Y. Hayashi:** None. **M. Tamaru:** None. **Y. Terao:** None. **K. Akagawa:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 117.04/C6

Topic: A.07. Developmental Disorders

Title: Effects of missense variations on the processing and function of synaptic adhesion molecule Neuroligin 4X

Authors: *M. KIMURA, T. YUMOTO, R. NAGATOMO, Y. NAO, T. TOMITA
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Abstract: Neuroligin (NL) proteins are postsynaptic cell adhesion molecules that bind to cognate presynaptic ligands, neurexin, and play important roles in formation and maturation of neuronal synapses. NL4X encoded by *NLGN4X* gene preferentially locates at inhibitory synapses and participates in the regulation of inhibitory synaptic plasticity. Several missense variations in *NLGN4X* gene have been implicated in the pathogenesis of neuropsychiatric disorders including X-linked mental retardation and autism spectrum disorder (ASD). However, pathogenic effects of these variations are largely unknown. We found that properly folded and glycosylated NL4X in endoplasmic reticulum is transported to the cell surface via Golgi apparatus. Then NL4X is processed by sequential proteolytic processing by metalloprotease and gamma-secretase in a similar fashion to that of NL1 (Suzuki et al., Neuron 2012). We systematically examined the metabolism and function of the NL4X proteins carrying missense variations. We found that several missense variants identified in ASD patients caused the defect in the folding, glycosylation and trafficking to the cell surface. Intriguingly, other rare variant that results in the L593F substitution increased the metalloprotease-mediated shedding, thereby reducing the cell surface level of NL4X. To investigate the effect of missense variations in the synaptogenic activity by NL4X in the primary neurons, we performed the synapse formation assay by coculture system. Disease-associated mutants as well as L593F variant failed to the accumulation of inhibitory presynaptic protein VGAT. Interestingly, these effects were recovered by treatment of chemical chaperone and metalloprotease inhibitor, respectively. These data indicate that genetic variations in *NLGN4X* gene affect the cell surface level as well as the synaptogenic activity of NL4X by multiple mechanisms.

Disclosures: **M. Kimura:** None. **T. Yumoto:** None. **R. Nagatomo:** None. **Y. Nao:** None. **T. Tomita:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 117.05/C7

Topic: A.07. Developmental Disorders

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International Exchange Scholarship for Ph.D candidates of Peking University

Title: Decoding the impacts of autism-associated de novo mutations, SAM and PDZ binding motif of EphB2 in neural development

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[1]SZ-PKU-HKUST Med. Ctr., Peking Univ., Beijing, China; [2]Shenzhen PKU-HKUST Med. Ctr., Shenzhen, China; [3]Immunol., Univ. of Connecticut Hlth. Ctr., Farmington, CT; [4]Materials Sci. and Engin., Johns Hopkins Univ., Baltimore, MD; [5]Div. of Life Sci., The Hong Kong Univ. of Sci. and Technol., Hong Kong, China

Abstract: Background: Autism is a highly complex neurodevelopmental disorder. Recent genetic studies identified two autism-associated de novo mutations on EphB2, including a de novo premature stop codon (Q858X) on the C terminus of kinase domain. Kinase domain-SAM-PDZ binding motif (KSP) truncation in EphB2 disrupted multiple neurodevelopmental events, including synapse density and spine formation. Eph receptors dimerization dynamics controls growth cone collapse by regulating Rho-GTPase. SAM-PDZ binding motif (SP) conserved across evolution. Truncation of SP domains in multiple EphA family members altered receptor dimerization propensity and kinase activity in various ways, indicating that KSP domains perform individual functions in signal transportation. However, the role of SP domains in EphB family is unclear. Mechanism of how SP regulates Eph receptor dimerization and the biological functions in neurodevelopment is still an unknown territory.
Methods: Kinase activity among Q858X mutation and EphB2 SP truncations were studied in HEK 293T, with or without ligand Ephrin B1 or B2 (R&D Systems) stimulation. pY594-EphB2 was detected by western blot as a kinase activity marker. EphB2 wild type (WT) and mutant plasmids with one pair of fluorescent resonance energy transfer (FRET) fluorophore were transfected into HEK cells for dimerization propensity study. Active Rho GTPase members were detected by western blot after transfection of EphB2 WT and mutants in HEK cells. Primary cultured mouse cortical neurons were transfected by lipofectamine 3000 at DIV0 and growth cone morphology were studied at DIV3. Statistical analysis was accomplished with SPSS 20.0.
Results: De novo mutation Q858X damaged pY594-EphB2, indicating kinase dead. EphB2 dSP increased pY594 significantly in a ligand stimulation independent manner, increased EphB2 dimerization propensity and decreased active RhoA expression level. However, Y931F mutation on SAM reduced pY594-EphB2 dramatically. Preliminary cortical neuron morphology results suggest dSP altered growth cone collapse dynamics.
Discussion: Eph as the largest tyrosine receptor kinase family in vertebrate regulates intercellular signals with high complexity. This study showed the conserved SP domains inhibits EphB2 dimerization and kinase activity, probably in a stereo-conformational inhibition manner. Further validations are ongoing. SP domains also modulated Rho GTPase dynamics which maybe the underlying mechanism of alteration in cortical neurons growth cone collapse. These results provide insight into how SP domains involve in orchestrating the Eph signaling transportation in neurodevelopment.

Disclosures: Y. Cai: None. **T. Light:** None. **J. Wan:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: NSERC

Title: Prostaglandin E2 regulates phosphorylation of spinophilin and growth cone morphology via PKA

Authors: *A. KISSOONDOYAL, D. A. CRAWFORD
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Abstract: Background: Lipids are major components of neuronal cell membranes and serve as a supply of signaling molecules, such as Prostaglandin E2 (PGE_2). Growing evidence indicates that PGE_2 signaling can influence formation of dendritic spines and affect neuronal plasticity. Recent studies have shown that in the brain, PGE_2 can influence the expression of a novel actin-bound protein called spinophilin. Phosphorylation of spinophilin by protein kinase A (PKA) regulates its binding to actin within dendritic spines of mature excitatory synapses.
Objective: This study investigates for the first time whether phosphorylation of spinophilin by PKA at ser94, known to reduce its affinity to actin, is PGE_2 dependent and if this may modulate growth cone morphology during early neuronal differentiation.
Methods: We differentiated neuroectodermal (NE4C) stem cells into neurons with serum-free media. The progression of differentiation was recorded and quantified every 48 hours using brightfield imaging system (Nikon Eclipse Ti-E microscope). Cells were treated with PGE_2 or forskolin following induction of differentiation. On days 6, 8, 10, and 12 of differentiation we examined growth cone turning and neurite length. Using real-time PCR and Western blot, we measured protein expression of total spinophilin and phosphorylated spinophilin (ser94).
Results: Our results show that initially on day 6 of differentiation, PGE_2 increased expression of spinophilin compared to untreated controls. However, as differentiation progressed (day 8-12) PGE_2 treatment significantly suppressed spinophilin expression. Interestingly, PGE_2 considerably increased the ratio of PKA-phosphorylated (ser-94) to total spinophilin relative to the untreated cells. The addition of PKA blocker (H89) decreased the level of phosphorylated spinophilin. The PKA-dependent mechanism was also confirmed with forskolin treatment. Furthermore, PGE_2 significantly affected growth cone morphology in a PKA-dependent manner. PGE_2 increased neurite length across differentiation, and reduced the number of growth cones turning with strongest effects observed earlier in differentiation (day 8).
Conclusions: This study demonstrates that PGE_2 can modulate the phosphorylation of the actin binding protein, spinophilin, as well as growth cone turning and neurite extension length via

PGE_2-PKA-dependent mechanism. This might have implications in developing brains considering that abnormal PGE_2 signaling is linked to neurodevelopmental disorders such as Autism. Prenatal changes in PGE_2 level due to genetic or environmental causes can influence early neuronal differentiation in the prenatal brain.

Disclosures: A. Kissoondoyal: None. **D.A. Crawford:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Program#/Poster#: 117.07/C9

Topic: A.07. Developmental Disorders

Support: Stanley Medical Research Institute

Title: Ubiquitination and degradation of adenylosuccinate synthetase, ADSS, is specified by the autism and schizophrenia associated CUL3 adaptor, KCTD13

Authors: *J. M. MADISON[1], K. DUONG[2], E. F. VIEUX[2], N. UDESHI[2], S. FERESHTIAN[2], K. PIERCE[2], C. CLISH[2], R. PLATT[2], F. ZHANG[2], S. CARR[2], E. M. SCOLNICK[2], J. R. COTTRELL[2]
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Abstract: Autism is a common, debilitating, and heritable neurodevelopmental disorder. Genetic analysis has identified a number of common and rare genetic variants that increase risk for this disorder. Among these identified variants is a locus at 16p11.2 spanning 27 genes, including *KCTD13*, which encodes a substrate adaptor of a CULLIN ubiquitin ligase. Ubiquitin ligases are protein complexes that promote the covalent addition of ubiquitin to other proteins, which may cause proteins to be targeted to the proteasome for degradation or may have other functional consequences. This KCTD13-CULLIN ubiquitin ligase also includes a subunit encoded by a gene, *CUL3*, which is also associated with risk for autism. The disease-association of these two ligase components suggests that substrates of the CUL3-KCTD13 ubiquitin ligase complex may play a role in autism, and identification of ligase substrates in neurons may provide insight into the pathogenesis of this disorder. Using quantitative proteomics in primary mouse neurons, we identified the protein adenylosuccinate synthetase (ADSS) as a putative substrate of the KCTD13 ubiquitin ligase. In mouse *Kctd13*-deletion neurons, ubiquitylation of ADSS is decreased, while protein abundance is increased. Our data suggest that ADSS is a direct substrate of a CUL3-KCTD13 ubiquitin ligase complex and that increased ADSS levels may alter cellular purinogenesis. This alteration in turn results in the production of a set of metabolites similar to adenylosuccinate lyase (ADSL) deficiency, an inborn error of metabolism that has autistic and epilepsy phenotypes. We will present the results of metabolic profiling of human 16p11.2

deletion fibroblasts and mouse *Kctd13* deletion neurons. These data suggest that autistic features of the 16p11.2 locus may be influenced by alterations of purine metabolism and reducing ADSS activity may have therapeutic benefit in autism patients with a 16p11.2 deletion.

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Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: HIAS15007 to J. A. F.

Title: Comparative expression analysis of autism-associated cadherin superfamily members

Authors: *J. A. FREI[1], G. J. BLATT[2], Y.-C. LIN[2]
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Abstract: Cell adhesion molecules (CAMs) play crucial roles in neural circuit formation. The cadherin superfamily is one of the largest families of CAMs containing more than one hundred molecules, including classical cadherins type I and II, protocadherins, and atypical cadherins. The type I classical cadherin N-cadherin is the most well-studied member to-date. Although there is only little known about the function of other cadherins, they have been strongly implicated in autism. A genome wide association study performed by the Hussman Institute for Human Genomics identified the classical cadherin type II CDH8, CDH9 and CDH11, the protocadherin family member PCDH9 and the atypical cadherin FAT1 as candidate risk genes. This suggests that cadherin signaling pathways could be disrupted and may display increased vulnerability in autism. As a first step toward understanding the central role of cadherins in the etiology of autism, we focused on CDH8, CDH11, PCDH9 as well as FAT1 and investigated the expression pattern of these cadherins in specific brain areas, cell types and their subcellular localization during development. This comparative expression analysis provides novel insights into common and distinct functions of these cadherins in neural circuit formation. Elevated expression levels of CDH8, CDH11 and PCDH9 in the same brain areas including cortex, hippocampus and thalamus/striatum were found. The relative expression levels in those brain areas varied depending on the developmental stage. In the cortex, cadherin expression peaked around P14. Consistent with this finding, cellular localization of CDH8 and CDH11 expression was observed in dendrites of 14 DIV cortical neurons. Synaptic plasma membrane fractionation revealed enrichment of CDH8, CDH11 and PCDH9 in synaptosomes, synaptic plasma

membrane and post-synaptic density. The expression pattern of FAT1 was distinct from the other cadherins as it was restricted to the cerebellum throughout postnatal stages. At the cellular level, FAT1 localized with MAP2-positive dendrites of cerebellar granule neurons. Our results revealed similar expression profiles among CDH8, CDH11 and PCDH9, with a distinct expression pattern for FAT1. The brain areas that revealed the highest cadherin levels overlap with those reported to be associated with autism. The temporal expression and the subcellular localization of cadherins are consistent with the proposed functions in synaptogenesis. Taken together, the present study highlights that cadherins of different subfamilies are expressed in a developmental time window and in brain areas implicated as vulnerable in autism. Support: Hussman Foundation grant #HIAS15007

Disclosures: **J.A. Frei:** None. **G.J. Blatt:** None. **Y. Lin:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: P7/2007-2013

Title: Modelling SHANK2-related autism using human induced pluripotent stem cells and derived neurons

Authors: *A.-K. LUTZ, M. DEMESTRE, T. M. BOECKERS
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Abstract: Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by deficits in social interaction and repetitive behavior. ASD comprise a heterogeneous spectrum of syndromic and non-syndromic forms of autism and rise by a variety of possible causes including environmental factors as well as genetic factors. Among these genetic factors, genes encoding the postsynaptic scaffolding ProSAP/SHANK protein family are interesting candidates, since up to 1% of all ASD patients have copy number variations or deletions in one of the *SHANK* genes, a considerable high number regarding the heterogeneity of the disease. Moreover, 0,17% of all ASD patients harbor variations in *SHANK2*. In this study, human induced pluripotent stem cell (hiPSC) lines were generated by reprogramming outgrowing keratinocytes from plucked human hair of a family originally described by Leblond et al. 2014. The family consists of father, mother and an affected child (patient) who harbors a *de novo* heterozygous deletion of 1.8Mb containing all exons of *SHANK2*. Generated hiPSC lines were characterized for pluripotency and found to fulfill all criteria demanded from pluripotent stem cells. Regarding expression of SHANK2, a nearly 50% reduction in mRNA expression and

approximately 25% less protein was found in patient-derived hiPSCs. We generated hiPSC-derived neuronal cells, in which a similar SHANK2 reduction was found. To study the consequences of this SHANK2 reduction, we screened the mRNA expression of synaptic proteins and transcription factors during neuronal development. In the patient-derived neurons, we found alterations that point towards an imbalance of excitatory and inhibitory signaling and disturbances in the expression of specific neuronal transcription factors. Multiple ASD-associated genes, for example MeCP2 and Neuroligins 1-4, are already described as putative causes for disturbances in GABAergic and glutamatergic circuits in the human brain. However, molecular effects of *Shank2* deletions have only been studied in rodent models so far, highlighting the importance of this study in human cells. Our data indicates disturbances in synaptic proteins in mature neuronal cells along with alterations in transcription factors essential for proper neuronal development. Thus, we provide evidence that neurons derived from hiPSCs harboring a heterozygous SHANK2 deletion serve as a suitable model to mimic an ASD-like phenotype, and to explore specific defects associated with this deletion.

Disclosures: **A. Lutz:** None. **M. Demestre:** None. **T.M. Boeckers:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: NIMH R00 MH102244

A NARSAD grant from the Brain Research Foundation

Title: Input-response dynamics of an autism-linked synaptic signalosome

Authors: *S. E. SMITH[1], E. A. BROWN[2]
[1]Ctr. for Integrative Brain Res., Seattle Childrens Res. Inst., Seattle, WA; [2]CIBR, Seattle Children's, Seattle, WA

Abstract: A key question facing autism researchers is how the hundreds of rare genetic autism risk factors fit into convergent biochemical pathways to produce the characteristic behavioral phenotypes of the disorder. Recently, several groups have proposed that neuronal activity-dependent signaling processes may be one such convergent pathway. We have applied Quantitative Multiplex co-Immunoprecipitation (QMI) to an interconnected protein network consisting of the protein products of 20 autism-linked genes that are physically localized to the glutamate synapse. QMI performs ~400 simultaneous co-immunoprecipitations and reports the fold-change of each dynamic protein-protein interaction in response to the experimental

stimulus, allowing network-scale modeling of protein complexes as they respond to synaptic inputs. In mouse neurons, we find that these ASD-linked proteins respond to activity by broadly changing their patterns of co-association. Moreover, distinct synaptic stimuli targeting ionotropic and/or metabotropic glutamate receptors (KCl, glutamate, NMDA and DHPG) each produce characteristic 'biosignatures': stereotypical, input-specific, network-scale rearrangements, suggesting an information-processing function. Weighted correlation network analysis reveals co-regulated modules of interactions that differentially respond to mGluR vs. NMDA receptor stimulation, and that sum together to produce a glutamate biosignature. Ongoing work is focusing on the contribution of known signaling second-messengers such as intracellular calcium or specific kinases to the overall network biosignature. Preliminary data suggests that calcium plays a major role in NMDA-responsive modules, but several examples of calcium-independent signals have also been identified. Our data suggest that this protein network constitutes a signalosome, a dynamic information-processing biochemical system. In the broader context of autism, we propose that this synaptic signalosome, composed of the protein produces of autism-linked genes, may be convergently disrupted in many different genetic forms of autism, and may represent an attractive 'druggable target' that is accessible and plastic throughout the lifespan.

Disclosures: S.E. Smith: None. **E.A. Brown:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: NIH NIMH F30MH108321-02

Title: Modelling synaptic mechanisms of autism-associated neuroligin-3 mutations using human neurons

Authors: *V. R. MIRABELLA[1], A. HAMOD[1], J. FANTUZZO[1], C. PAK[2], T. C. SUDHOF[2], D. COMOLETTI[1], Z. P. PANG[1]
[1]Neurosci. and Cell Biol., Child Hlth. Inst. of NJ, Rutgers-Rwjms, New Brunswick, NJ;
[2]Stanford Univ., Stanford, CA

Abstract: Synaptic transmission controls information flow in the brain and synaptic dysfunction is likely a biological basis for several neurodevelopmental disorders including autism spectrum disorders (ASDs), Down syndrome, and neuropsychiatric disorders such as schizophrenia. Recent human genetic studies revealed that an increasing number of mutations in neuroligins (NLGNs) and neurexins, synaptic cell-adhesion proteins, are linked to ASDs and schizophrenia. The first defined gene mutation identified in idiopathic autism was an arginine (R) to cysteine

(C) missense mutation at position 451 of NLGN 3 (NLGN 3 R451C). Numerous studies using knock-in animals and heterologous overexpression systems have suggested that NLGN 3 R451C may act as both a loss and gain-of-function mutation, however the detailed molecular mechanism(s) by which it causes behavioral pathology and synaptic dysfunction remain unclear. Recent advances in stem cell biology have allowed the efficient conversion of human stem cells into defined neural subtypes and we hypothesized that studying the R451C mutation using this simplified and species-specific approach may yield new insight into its molecular etiology. To test this hypothesis, we have generated isogenic knock-in human embryonic stem cell lines harboring NLGN 3 R451C and an additional putative loss-of-function frameshifted NLGN 3 allele. Surprisingly, cultured R451C human neuronal cells exhibited a previously unidentified enhanced synapse formation phenotype, but no gross changes in neuronal membrane properties, excitability or neurite outgrowth, suggesting that this effect is selective and not due to a general increase in neuronal maturation. Furthermore, human neuronal cells harboring the loss-of-function allele also exhibited a significant increase in synapse formation indicating the phenotype is, at least in part, likely due to a loss of NLGN 3 gene function rather than a gain-of-function effect produced by the R451C missense mutation. Ongoing experiments are defining the correlating functional and biochemical parameters in both excitatory and inhibitory human induced neurons to determine the molecular basis for these observations.

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Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: Hussman Foundation HIAS15003 grant to Yu-Chih Lin

Title: An autism-associated mutation in CEP290 disrupts Shh-signaling, impairs regulation of ciliary protein mobility and affects cell proliferation

Authors: *M. B. KILANDER, Y.-C. LIN
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Abstract: Recent advances in genetic sequencing have greatly expanded the set of mutations and chromosomal alterations suspected to play a role in the progression of autism. However, the spatiotemporal mechanisms by which the products of this altered genetic material act to impede normal neurodevelopmental processes are to-date largely unknown. Results from whole exome sequencing from individuals with autism identified mutations in the centrosomal protein CEP290

which is a crucial component in the formation and function of the primary cilium. CEP290 is a major ciliopathy risk gene, e.g. in Joubert Syndrome, Meckel Syndrome and Bardet-Biedl Syndrome. Interestingly, defects in cerebellar development and autistic traits are occasionally observed in these ciliopathy patients. The primary cilium is a microtubule-rich cell protrusion important for cell proliferation, differentiation and migration. Moreover, the primary cilium serves as the confined compartment for selective cell signaling and for cell-environment communication. Sonic Hedgehog (Shh) signaling, a biological pathway necessary for proper tissue development and maintenance, is preferentially localized to the primary cilium and is essential for proliferation of granule cell progenitors (GCP) during cerebellar development. However, to-date not much is known about the role of the primary cilium in neurodevelopment and in the establishment of mature neural circuits. Consequently, how CEP290 plays a role in regulating brain function is still unclear.
In the present study we examined the effects of autism-associated *CEP290* mutations on a cellular level and focused our investigation on the molecular aspects of Shh signaling regulation. A battery of imaging analysis methods were used to assess changes in primary cilium-dependent cellular processes in NIH/3T3 cells overexpressing of CEP290 WT and mutated constructs. We found that one of the missense mutations, R1747Q, generated a defects response to Shh, failed to regulate normal localization of the Shh receptor Smoothened (Smo), changed the mobility of ciliary proteins, e.g. Arl13b, and altered cell proliferation.
In summary, our investigation describing the cellular mechanisms affected by a specific autism-associated mutation in the *CEP290* gene provides novel information on the role of the primary cilium in regulating tissue development in neurological conditions.

Disclosures: M.B. Kilander: None. **Y. Lin:** None.

Poster

117. Cellular and Molecular Mechanisms of Autism

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Topic: A.07. Developmental Disorders

Support: NS034007

NS047384

Title: Functional screen of autism-assocaited single nucleotide variants in genes encoding translational machinery

Authors: *A. G. VOROBYEVA[1], I. IOSSIFOV[2], T. E. DEVER[3], E. KLANN[4]
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Harbor, NY; [3]Natl. Institue of Child Hlth. and Human Develop., Bethesda, MD; [4]Ctr. for Neural Sci., New York Univ. Ctr. for Neural Sci., New York, NY

Abstract: Autism spectrum disorder (ASD) is a heritable neurodevelopmental disorder characterized by the early onset of social and communication deficits, repetitive behaviors, and cognitive inflexibility. Although several monogenic syndromes with a high incidence of ASD have been well characterized, these only account for a small portion of all ASD cases. Therefore the majority of ASD genetic risk factors and causative genes are still elusive. Multiple lines of evidence suggest that dysregulated translational control is one molecular underpinning of ASD. We searched the exome sequencing data of Simons Simplex Collection families with a child affected by autism for single nucleotide variations (SNVs) in genes encoding proteins that make up the eIF2 translation initiation signaling network and found numerous ultra rare heritable and *de novo* autism-associated SNVs. Therefore, we hypothesized that these ultra rare heritable and *de novo* missense and nonsense ASD-associated SNVs in genes encoding components of the eIF2 signaling network would disrupt their protein structure and function, leading to dysregulated translation initiation resulting in abnormal development and cognitive function. Using bioinformatics and cell-based assays we screened >40 ASD-associated SNVs. Our cell-based assays showed several Loss-of-Function (LoF) mutations in *EIF2AK4*, *EIF2AK3,* and *EIF2AK2* which encode the eIF2α kinase GCN2, PERK, and PKR respectively, dysregulate global protein synthesis. Because LoF *EIF2AK4, EIF2AK3* and *EIF2AK2* mutations should result in carrier haploinsufficiency for eIF2α kinases, we examined *Eif2ak4*$^{+/-}$, *Eif2ak3*$^{+/-}$ *or* *Eif2ak2*$^{+/-}$ mice. Both PERK$^{+/-}$ and GCN2$^{+/-}$ mice displayed a range of cognitive dysfunction and ASD-like behaviors. Surprisingly we observed distinct behavioral impairments in *Eif2ak4*$^{+/-}$ and *Eif2ak3*$^{+/-}$ mice suggesting eIF2α kinases may play a unique and indispensable role in various brain regions and/or neuronal subtypes governing specific behaviors. In addition, we found two ASD-associated mutations in the *EIF2S1* gene that encodes eIF2α subunit. Characterization studies of the *EIF2S1* mutations are currently ongoing, but our preliminary data indicate that at least one ASD-associated mutation alters the eIF2 heterotrimer, disrupts global protein synthesis, and alters neuronal morphology. Taken together, our findings suggest that heritable and *de novo* LoF ASD-associated SNVs in the eIF2 signaling network disrupt protein synthesis and give rise to phenotypes consistent with intellectual disability and ASD, implicating aberrant eIF2 regulation in abnormal neurodevelopment. Supported by NIH grants NS034007 and NS047384.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: MH060163

MH097093

Title: Fragile X circuits show differential developmental delays of spontaneous and evoked network activity but normal homeostatic plasticity

Authors: *H. MOTANIS[1], D. V. BUONOMANO[2]
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Abstract: Since the generation of the first mouse model of Fragile X (FX) syndrome a broad range of neurophysiological phenotypes have been reported. However, it remains unclear which phenotypes are casually related to the cognitive deficits associated with FX and which are an indirect consequence of abnormal development or experience. FX syndrome is characterized by developmental delays, and recently we have demonstrated an *in vitro* developmental delay of spontaneous Up state activity (Motanis et al., 2015)—suggesting that this neural phenotype is a direct consequence of the FX mutation as opposed to an indirect product of compensation or abnormal development. Here we use two different *in vitro* approaches (whole cell recording and calcium imaging of cortical cultures) to further characterize spontaneous and evoked activity and to determine whether FX circuits adapt normally to chronic external inputs. We first determined whether evoked activity was different in WT and FX circuits at different developmental ages using whole-cell recordings. At 11-15 days in vitro (DIV) evoked EPSP strength was not different between WT and FX cortical circuits, however evoked network activity was significantly reduced in FX circuits ($p<0.01$). At 25-30 DIV WT circuits exhibited a developmental change in synaptic strength as evidenced by an increase in the asymptote of the input-output curves, EPSPs in FX circuits, however, were significantly weaker ($p<0.005$). By 35-40 DIV there were no differences in EPSPs strength or evoked network activity between WT and FX circuits—indicating that evoked activity is developmentally delayed in FX circuits.
Next we explored network-level plasticity, by examining activity-dependent modulation of evoked activity. We used chronic optogenetic stimulation (COS) to emulate an increase in externally driven activity and induce homeostatic plasticity of network activity. WT and FX slices were stimulated for two days at 25-30 or 35-40 DIV. COS resulted in significant reduction of evoked EPSP strength ($p<10\text{-}7$, $p<0.05$), with no genotype difference. These results indicate that FX circuits exhibit normal homeostatic plasticity and suggest that some previously described neural phenotypes observed in FX may be compensatory.
Two-photon calcium imaging recording confirmed previous observation that spontaneous activity between WT and FX circuits were not different at 25-30 DIV. Two-photon calcium imaging allowed us to record from all layers of the cortex and determine that during Up states some “trigger” neurons were consistently activated before others. We are currently examining whether FX circuits exhibit deficits in a form of temporal in vitro learning.

Disclosures: H. Motanis: None. **D.V. Buonomano:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Support: CIHR

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Title: Regulation of Kv4 potassium control of granule cell excitability by FMRP and ERK1/2

Authors: *X. ZHAN[1], G. SAHU[1], H. ASMARA[1], C. SZALAY[1], G. ZAMPONI[2], R. W. TURNER[2]
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Abstract: The excitability of cerebellar granule cells is strongly regulated by an ion channel complex consisting of Cav3 (T-type) calcium and Kv4 (A-type) potassium channels (Cav3-Kv4). We recently found that long-term potentiation of mossy fiber input to granule cells involves a dramatic increase in postsynaptic excitability through an ERK-mediated phosphorylation and reduction in A-type current. The reduction in A-type current derives from a hyperpolarizing shift in Kv4 voltage for inactivation (Vh) and activation (Va) that depends on joint mGluR/NMDAR activation and ERK-mediated phosphorylation. This study examined how regulation of Cav3 and Kv4 channels could contribute to disorders of synaptic plasticity in the Fragile X Syndrome (FXS) model of Autism Spectrum Disorder. FXS derives from a loss of FMRP, a key regulator of protein translation that includes Cav3, Kv4, and ERK kinase, with abnormally high levels of ERK in FXS. We found that ERK1/2 phosphorylates both Cav3.1 and Kv4.3 in rat cerebellum but not KChIP3, the calcium sensor of the Cav3-Kv4 complex. Direct infusion of activated ERK (pERK) through a patch recording electrode evoked a hyperpolarizing shift in Vh of Cav3.1 and Kv4.3 in tsA-201 cells and granule cells of wt animals. Moreover, FMRP coimmunoprecipitated (coIP) with both Cav3.1 and Kv4, but with loss of the Cav3.1-FMRP association at 50 µM [Ca], a physiologically relevant elevation of [Ca]i. Infusion of FMRP through a recording electrode again shifted Va and Vh of Cav3.1 channels in tsA-201 cells and Kv4 in granule cells. These findings are important in revealing a previously unrecognized association between FMRP and both Cav3 calcium and Kv4 potassium channels that has a direct influence on biophysical properties at the plasma membrane level. The loss of FMRP in FXS predicts important effects on the ability for granule cells to process mossy fiber input that will be determined through studies of granule cell excitability in wt vs FXS animals.

Disclosures: X. Zhan: None. **G. Sahu:** None. **H. Asmara:** None. **C. Szalay:** None. **G. Zamponi:** None. **R.W. Turner:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

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Topic: A.07. Developmental Disorders

Support: Partial support provided by NIH Grant R01MH071376

Title: Neonatal stimulation of PKC epsilon signaling normalizes Fragile X-associated deficits in PVN oxytocin expression and later-life social and anxiety behavior

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Abstract: Fragile X Syndrome (FXS) is an inherited developmental disorder characterized by disturbances in emotional and social behavior. Our studies have revealed suppressed hippocampal PKCε expression in Fmr1 knockout (KO) mice, the leading model of FXS. To compensate for this deficiency in PKCε expression, we stimulated PKCε in neonatal mice by administering a selective PKCε activator, dicyclopropyl-linoleic acid (DCP-LA), and studied its effect on hippocampal neurons and a proximal target of the hippocampus, the hypothalamus, which regulates social and emotional behavior. We observed that at postnatal day 18 (P18), the KO mice displayed increased surface localization of the 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR2 in the CA1 region, indicative of increased excitability within the hippocampus. Since the hippocampus is known to exert an inhibitory influence on the hypothalamus, we tested if this possible CA1 stimulation was associated with a suppression of oxytocin synthesis in the hypothalamus. Intriguingly, in the number of oxytocin+ cells in the paraventricular nucleus (PVN) of P20 KO mice was sharply suppressed. Furthermore, the increased surface localization of GluR2 and the suppression of oxytocin+ cells in the KO mice were rescued by DCP-LA treatment from P6-14, to levels comparable to that in the wild-type controls. Finally, neonatal DCP-LA treatment rescued hyper-anxiety and social behavior deficits in adult (>P60) KO mice. Thus, we present a novel strategy to circumvent aberrant brain development in FXS and accompanying behavioral deficits, by activating PKCε signaling during neonatal development.

Disclosures: A.E. Marsillo: None. **B. Gerges:** None. **S. Menkes:** None. **A. Chatterjee:** None. **R. Sadek:** None. **A. Mancuso:** None. **C. Dobkin:** None. **K.K. Chadman:** None. **P. Banerjee:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH106490

Title: Experimental manipulation of astroglial FMRP levels alters synaptic activity and behavior phenotypes in FXS mouse models

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Abstract: Fragile X syndrome (FXS) is a developmental intellectual disability caused by the loss of fragile X mental retardation protein (FMRP) function. The loss of FMRP, particularly in post-synaptic neurons, abolishes its repressive function on protein synthesis, contributing to altered synaptic activity and behavior phenotypes observed in mouse models of FXS and FXS patients. Recently, accumulating evidence has begun to demonstrate that non-post-synaptic expression of FMRP plays important roles in the pathogenesis of FXS. We recently generated inducible astroglia-specific Fmr1 conditional knock-out (i-astro-Fmr1-cKO) and restoration (i-astro-Fmr1-cON) mouse models in which the *fmr1* allele is selectively disrupted or restored in astrocytes, respectively. We showed that selective deletion of astroglial FMRP plays a primary role in GLT1 reduction in FXS *in vitro* and *in vivo*. In the current study, we investigated whether the selective loss or restoration of FMRP in astrocytes affects synaptic activation and typical FXS-related behavior phenotypes. We first measured the mEPSC of layer 5 pyramidal neurons in i-astro-Fmr1-cKO and i-astro-Fmr1-cON mice. Although the frequency of mEPSC in these mice is not significantly different from their respective control mice, the mEPSC amplitude is significantly increased in cKO mice compared to control and is reversed in cON mice. We then recorded synaptic AMPAR and NMDAR currents and calculated AMPA/NMDA current ratio of individual neurons and found a significantly decreased AMPA/NMDA current ratio in cKO mice, especially at older (P38-45) but not in younger (P21-27) age. In some patched neurons, NMDAR currents are significantly increased in cKO compared to control slices, while AMPAR currents are highly similar. We observed similarly decreased AMPA/NMDA ratio in Fmr1 KO mice. Selective re-expression of FMRP in astrocytes, however, reversed the decreased AMPA/NMDA current ratio. Encouraged by physiological changes in cKO and Fmr1 KO mice, we performed the open field test on these mice. We observed significantly increased total running distance within 12 minutes in the open field chamber with cKO mice when compared to control mice (P30-40), suggesting that the selective loss of astroglial FMRP is sufficient to induce hyperactivity. Importantly, this hyperactivity phenotype is rescued in cON mice

compared to control. We are currently testing the social interaction phenotypes in i-astro-fmr1-cKO and i-astro-fmr1-cON mice. These results suggest that astroglial FMRP levels sufficiently modulate synaptic activation and behavior phenotypes in mouse models of FXS.

Disclosures: Y. Yang: None. **H. Higashimori:** None. **C. Schin:** None. **M. Chiang:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NIH/NEI T32-EY13933-16

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NIH/NEI R01 EY12736-27

Title: Glial-mediated synaptic refinement in a mouse model of Fragile X syndrome

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Abstract: Fragile X Syndrome (FXS) is the leading monogenic cause of autism and intellectual disability and results from the silencing of the *Fmr1* gene, which codes for the translational regulator, FMRP. FXS is characterized by structural and functional defects at the synapse, specifically long, thin dendritic spines and aberrant LTD. Structural defects in axons have also been observed. Glia are known regulators of synapse growth and elimination. Despite FMRP expression in glia and reports of glial defects such as altered astrocytic glutamate signaling in FXS, little is known about glial function and dysfunction in FXS. Our lab has identified a defect in glial phagocytosis in the *Drosophila* model of FXS. This is associated with decreased levels of activated glia, marked by expression of Draper, the *Drosophila* homolog of the mammalian astrocyte phagocytic receptor, MEGF10. Whether such a defect occurs in vertebrates is unknown.
The mouse retinogeniculate projection is a classic system in which to study synapse refinement. As retinal ganglion cell (RGC) axons extend from each eye to the dorsal lateral geniculate nucleus (dLGN), their arbors and synapses from opposite side (contralateral) and same side (ipsilateral) eyes overlap. During the first postnatal week, excess branches and synapses are refined. By postnatal day 10 (P10), each dLGN neuron only receives inputs from a single eye—either contralateral or ipsilateral. Both microglial and astrocytic phagocytosis are known to participate in this synapse refinement. We are investigating the role of glial phagocytosis in

synapse refinement in the mouse retinogeniculate system in FXS. We first examine gross synaptic refinement in the retinogeniculate system of the *Fmr1* KO mouse by labeling RGCs from each eye with anterograde tracers (CTB) conjugated to different fluorophores and quantifying the extent of ipsilateral and contralateral overlap in the *Fmr1* KO mouse as compared to WT littermates. *Fmr1* KO refinement is enhanced in the first postnatal week (P7) compared to WT. At P14, refinement in the *Fmr1* KO mutant is comparable to WT, but by adulthood (P40), retinogeniculate inputs are less refined in the *Fmr1* KO dLGN than in WT. To investigate whether these biphasic alterations in refinement are driven by astrocyte-mediated phagocytosis of synapses, we generated an astrocyte-labeled *Fmr1* KO mouse (*Fmr1* KO;Aldh1l1-eGFP). In combination with CTB-labeling of RGCs, we are assessing astrocytic engulfment of presynaptic inputs in the *Fmr1* KO mouse. This work will help to advance our understanding of the role of FMRP in glial function and will elucidate the role of glia in development and adult-stage refinement of the visual system.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Title: Altered structure-function relationship of dendritic spines in the developing somatosensory cortex in a mouse model of Fragile X Syndrome

Authors: *S. A. BOOKER[1,2,3], O. R. DANDO[1,2,3], A. P. F. DOMANSKI[4,1], J. T. R. ISAAC[5], G. E. HARDINGHAM[1,2,3], D. J. A. WYLLIE[1,2,3], P. C. KIND[1,2,3]
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Abstract: Fragile X Syndrome (FXS) is a neurodevelopmental disorder which can lead to intellectual disability, epilepsy, and tactile hypersensitivity in patients. The mouse model of FXS (*Fmr1*$^{-/y}$) displays impaired synaptic function, which may explain features of this disease. Excitatory synaptic transmission in mature neurons occurs at dendritic spines which show normal density and only nanoscale differences in structure in the *Fmr1*$^{-/y}$ mouse. *Fmr1*$^{-/y}$ mice are exemplified by enhanced neuronal circuit activity, which is at odds with perceived reduced synaptic function. Given that FXS patients and the *Fmr1*$^{-/y}$ mouse model both have sensory hypersensitivity; the somatosensory cortex may be an ideal target to identify the synaptic mechanisms underlying FXS. Despite this, little is known of the function of spines in *Fmr1*$^{-/y}$ mice, nor how they integrate in a spatiotemporal manner driving neuronal output. To address this we have examined the structure and function of dendritic spines on the principal excitatory (stellate) cells in the juvenile somatosensory cortex.
We combined 2-photon photolysis of caged-glutamate with correlated super-resolution STED imaging to show that while spine density and shape are unaffected by the loss of FMRP, single spine synaptic currents are larger in FXS mice, have higher NMDA:AMPA ratio, with more "silent" spines. These observed synaptic alterations may result from the increased incidence of individual spines forming synaptic contacts with multiple independent presynaptic boutons, which is accompanied by increased frequency of NMDAR miniature synaptic events. In *Fmr1*$^{-/y}$ mice we show that dendritic spines on somatosensory stellate cells show excessive dendritic summation in response to near simultaneous photolysis of caged glutamate at multiple spines leading to increased dendritic gain. This enhanced dendritic summation is due, at least in part, to lowered HCN-mediated currents, which also contribute to the altered intrinsic physiology of somatosensory stellate cells in the *Fmr1*$^{-/y}$ mouse. We show for the first time that somatosensory neurons in FXS mice display altered input and output function giving rise to local hyperexcitability and aberrant sensory processing. These findings provide a plausible explanation for sensory hypersensitivity observed in FXS patients, and may provide potential therapeutic targets.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NINDS Grant RO1NS065992

NIMH Grant R01MH109026

Title: Impaired synaptic scaling but intact homeostatic intrinsic plasticity in cortical neurons from FMR1 KO mice

Authors: *P. BUELOW[1,2,3], G. J. BASSELL[2], P. A. WENNER[3]
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Abstract: Patients with Fragile X Syndrome (FXS), the most common cause of heritable intellectual disability and the leading cause for autism spectrum disorder, experience a wide range of debilitating symptoms, from sensory hypersensitivity and seizures to sleep disturbances. Foundational studies in a mouse model of FXS, the Fragile X Mental Retardation 1 (*FMR1*) KO, suggest that an impaired excitatory/inhibitory (E/I) balance may underlie symptoms associated with FXS. The E/I balance would be expected to depend on homeostatic plasticity mechanisms, which act to stabilize network activity levels. Consistent with this idea, one form of homeostatic plasticity, called synaptic scaling, is absent in hippocampal organotypic slice cultures from *FMR1* KO mice. Synaptic scaling is defined by a multiplicative increase or decrease of all miniature postsynaptic current (mPSC) amplitudes in a neuron, and is thought to be in place to maintain network spiking activity following network activity-perturbation, for example by concurrently blocking the sodium voltage-gated channels with TTX and the NMDA receptors with APV. Consistent with previous hippocampal studies, we now show that AMPAergic synaptic scaling is also absent in ~DIV 12 *FMR1* KO primary cortical neurons following 48 hour treatment with TTX and APV. Thus, impaired synaptic scaling may also significantly contribute to the deficits previously reported in *FMR1 KO* cortical circuitry. The finding that synaptic scaling is absent in cortical *FMR1* KO neurons, motivated us to assess whether other homeostatic mechanisms may be perturbed. Homeostatic intrinsic plasticity regulates network excitability levels by adjusting intrinsic cellular excitability levels in a homeostatic fashion, e.g. through Na^+ channel insertion following spike blockade. We hypothesized that homeostatic intrinsic plasticity might be relied upon to a greater extent in cortical *FMR1* KO neurons to compensate for the lack of AMPAergic scaling. We followed the same activity perturbation protocol as for synaptic scaling (TTX+APV 48 hr) and measured threshold voltage/current and instantaneous firing frequencies in *FMR1* KO and WT neurons, which reflect the excitability level of a neuron. We found that homeostatic intrinsic plasticity is intact in *FMR1* KO primary cortical neurons at ~DIV 12. This finding supports our hypothesis that *FMR1* KO cortical neurons rely more on homeostatic intrinsic plasticity mechanisms to maintain a stable network activity level than WT neurons. Ongoing work in the lab is exploring this hypothesis further using multi-electrode arrays.

Disclosures: **P. Buelow:** None. **G.J. Bassell:** None. **P.A. Wenner:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Title: Transcriptome interrogation in the dysregulated central amygdala of juvenile Fmr1 KO mice

Authors: *M. H. DAVENPORT, R. A. BECKER, S. E. FITZPATRICK, C. K. ROBINSON, T. L. SCHAEFER, C. A. ERICKSON
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Abstract: Many of the fragile X syndrome (FXS) clinical phenotypes, including hypersensitivity to auditory stimuli and seizure susceptibility, are recapitulated in the *Fmr1* knock out (KO) mouse model of the disorder. Extracellular signal-regulated kinase (ERK; active when phosphorylated) has long been implicated in FXS pathophysiology and basal levels of ERK activation have been shown to be increased in brain regions important for fear processing and cognition. ERK signaling is thought to be a convergence point for a variety of altered cellular signaling cascades and is used as an indication of aberrant cellular signaling in both mouse and human studies. In normal behaving rodents, cell-type and region-specific coordination ERK activation and deactivation is known to be required for a variety of behaviors, with activation associated with neuronal activity. Here, we show an increased number of phosphorylated ERK (pERK) positive cells in the central amygdala (CeA; main output center of the amygdala) with no differences in the lateral amygdala (LA; main input center of the amygdala) in behaviorally naïve juvenile *Fmr1* KO mice compared to wild type littermates. However, immediately following an audiogenic seizure (AGS) paradigm, ERK is dramatically deactivated in the CeA and hyper-activated in the LA of *Fmr1* KO mice that experience tonic/clonic seizure activity compared to both WT and *Fmr1* KO mice that do not seize. These data indicate that region-specific alterations in neuronal activity within the amygdala may contribute to AGS susceptibility. Furthermore, ERK phosphorylation following behavioral challenge may be a more informative indicator of circuit level defects in the *Fmr1* KO brain than basal pERK observations. As both dynamic regulation of amygdalar ERK and CeA activity are required for the formation and consolidation of fear memory, we performed fear conditioning experiments, but found no phenotype in the acquisition/presentation of cued or contextual fear memories in juvenile *Fmr1* KOs. To explore molecular phenotypes in the juvenile *Fmr1* KO CeA which may contribute to its altered activity during AGS, we performed RNA-seq from CeA tissue punches. While this analysis identified few differentially expressed genes, analysis of gene ontologies and KEGG pathways revealed significant alterations in various processes such as activity dependent intracellular signaling cascades including the ERK pathway and synapse structure and stability.

Given this evidence for a synaptic phenotype in the CeA, studies are ongoing utilizing Golgi-Cox stain to describe any alterations in dendritic spine density or morphology.

Disclosures: M.H. Davenport: None. **R.A. Becker:** None. **S.E. Fitzpatrick:** None. **C.K. Robinson:** None. **T.L. Schaefer:** None. **C.A. Erickson:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NIH Grant MH090237

Title: Widespread conservation of axonal fragile X granules in the adult mammalian hippocampus

Authors: K. A. SHEPARD, L. I. T. KORSAK, D. LE, *M. R. AKINS
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Abstract: Local axonal protein synthesis plays critical roles in the formation and plasticity of neuronal circuits. Understanding the roles of this mechanism requires identifying circuits that contain axonal ribonucleoprotein particles (RNPs) and how these vary across development. Fragile X granules (FXGs) are axonal RNPs found in a stereotyped subset of mature axons in the intact brain that contain the Fragile X protein and translational regulator FMRP along with mRNA and ribosomes. Remarkably, the developmental pattern of FXG expression in hippocampus is species-dependent. In adult humans and rats, FXGs are found in the hippocampus in both dentate mossy fibers and CA3 associational fibers. In contrast, in adult mice, FXGs are absent from hippocampal axons despite their presence in hippocampal circuits in juvenile mice. To better understand this species-dependent FXG expression, we examined adult hippocampus from species representing a broad variety of mammalian taxa separated by up to 160 million years of divergent evolution. We found FXGs in adult hippocampus in mammalian species that are distantly related, including prosimians (treeshrews), Xenarthra (armadillos), and marsupials (opossums). Within rodents, we found FXGs in adult hippocampus of voles, deer mice (*Peromyscus*), and rats. In contrast, we did not observe FXGs in adult hippocampus in a total of eight lab-adapted and wild-derived *Mus musculus* strains, including members of both the *domesticus* and *castaneus* subspecies. Since FXGs were found in adult hippocampus of animals raised in animal colonies (including rats, *Peromyscus*, and opossums), adult FXG expression does not require exposure to an enriched or natural environment. Further, adult FXG expression does not obviously correlate with body size. Instead, adult hippocampal FXGs and their associated translational machinery seem to have been selectively lost in the mouse lineage

sometime after mice and rats diverged. FXG-regulated axonal translation therefore appears to be a broadly conserved mechanism for regulating the axonal proteome in mature axons in the adult mammalian hippocampus.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NIH Grant HD082013

Title: Dysregulation of mTOR -p70-S6K1 signaling in fragile X syndrome hiPSC-derived neural cells

Authors: *M. KALINOWSKA[1], N. RAJ[2], G. J. BASSELL[2], E. KLANN[1]
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Abstract: Fragile X syndrome (FXS) is a common genetic cause of autism spectrum disorder (ASD) and intellectual disability resulting from a mutation in fragile X mental retardation protein (FMRP). The mutational basis of this disorder is abnormal trinuclotide CGG repeat expansion in the 5' untranslated region of the *FMR1* gene, leading to its silencing and lack of FMRP expression. FMRP is an mRNA binding protein with functions in mRNA transport, localization and translation. Thus, mRNA translation is altered in FXS and many studies strongly link this elevated translation to pathophysiology of FXS, including abnormal synaptic function and morphology. Neurodevelopment is also altered in *Fmr1* KO mouse, a model of FXS, as evidenced by presence of abnormally immature dendritic spines and delayed circuit maturation (Pan, 2010, Harlow, 2010). However, due to differences in nervous system development between humans and mice, *Fmr1* KO mouse model may not fully recapitulate human neural development. In addition, *FMR1* gene epigenetic silencing that causes FXS occurs only in humans (Brouwer 2007). We used induced pluripotent stem cells (iPSCs) derived from FXS and normal control subject fibroblasts to study neurodevelopment in FXS. We examined signaling by mechanistic target of rapamycin (mTOR) and protein synthesis during neural differentiation of hiPSCs to neural precursor cells and neurons. MTOR, a serine/ threonine kinase, is a master regulator of cell growth that integrates diverse signals to promote protein synthesis and its activation is elevated in *FMR1* KO mouse brain (Huber 2015). Activation of p70-S6K1 (S6K1), a downstream target of mTOR, is also enhanced in FXS mouse model, and genetic or pharmacological targeting of S6K1 can ameliorate biochemical, behavioral and morphological phenotypes in FXS mouse model (Bhattacharya 2012, 2016). We observed enhanced activation

of S6K1 and its downstream targets in FXS iPSC-derived neural cells. In addition, basal protein synthesis was perturbed in FXS cells and treatment with PF-4708671, an isoform-specific inhibitor of S6K1, normalized S6K1 activation and protein synthesis. Future studies will determine the effects of perturbed mTOR -S6K1 signaling on neural cell development and neurogenesis in FXS cells, as mTOR signaling plays important roles in neural stem cell differentiation and development.

Disclosures: **M. Kalinowska:** None. **N. Raj:** None. **G.J. Bassell:** None. **E. Klann:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: MH090237

Title: Fragile X Granules localize to nociceptive and motor axons in the mouse spinal cord

Authors: *M. MITCHELL[1], S. SINGH[2], C. MCMILLAN[2], M. R. AKINS[3]
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Abstract: Axonal protein synthesis is important for the formation, plasticity, and regeneration of neuronal circuits. This local translation is regulated in a circuit-dependent manner by axonal ribonucleoprotein particles (RNPs) that contain RNA binding proteins such as FMRP, the protein mutated in the autism-related disorder Fragile X syndrome (FXS). FXS is characterized by a constellation of symptoms including both motor and sensory deficits that arise from dysregulated neuronal protein synthesis. FMRP is a constituent of circuit selective axonal RNPs termed Fragile X granules (FXGs) that also contain the FMRP related proteins FXR1P and FXR2P. FXGs are exclusively localized to axons that have synaptically integrated into circuits where they associate with ribosomes and mRNA and influence the composition of the axonal proteome. These granules exhibit circuit-dependent protein composition, with FMRP a constituent of forebrain FXGs but absent from most hindbrain FXGs. Whether FXGs are also found in axons in spinal cord circuits has not been examined. To begin addressing whether FXG-regulated axonal translation may contribute to spinal cord function, we examined spinal cords from mice ranging in age from 15 days old to three months old. FXGs were expressed in spinal cord circuits across this range, with particularly robust expression in 30 day old animals. We therefore further investigated their localization within spinal cord axons in mice at this age. FXGs were most prevalent in alpha-motor neuron axons innervating the ventral roots as well as in primary and second order nociceptive afferents. Investigation of FXG protein composition revealed that all spinal cord FXGs contain FMRP, similar to the FXGs in the forebrain. As with brain FXGs,

ribosomes were found in association with all populations of spinal cord FXGs. Consistent with past observations in forebrain, FMRP negatively regulates FXG abundance in spinal cords as preparations from *Fmr1* null mice exhibit an increased density of FXGs. Together, these findings suggest that FXG-regulated axonal protein synthesis contribute to nociceptive and motor function in the spinal cords. Moreover, dysregulation of this axonal translation may contribute to sensory and motor deficits observed in Fragile X patients.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Title: Mitochondrial alterations in a mouse model of Fragile X syndrome

Authors: S. D'ANTONI[1], L. DE BARI[2], M. BORRO[3], D. VALENTI[2], C. M. BONACCORSO[4], M. SPATUZZA[1], M. SIMMACO[3], R. A. VACCA[2], *M. CATANIA[1]
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Abstract: Fragile X syndrome (FXS) is the most common form of hereditary mental retardation and results from the absence of Fragile X mental retardation protein, an RNA-binding protein that regulates the translation of several mRNAs. By a comparative proteomic analysis of cortical synaptosomes of 21 days old wild-type and *Fmr1* knockout (KO) mice, a model of FXS, we found twenty-one differently expressed proteins, including up-regulated mitochondrial glycerol-3-phosphate dehydrogenase (mG3P-DH), a key component of the glycerophosphate shuttle. Furthermore, an increased activity of mG3P-DH and of all mitochondrial respiratory chain complexes was detected in *Fmr1* KO mouse cortex at different ages, whereas no change occurred in the activity of cytoplasmic glycerol-3-phosphate dehydrogenase and key glycolytic enzymes. We show for the first time that in FXS the activities of mitochondrial enzymes are increased, suggesting a possible mitochondrial hyper-activation that could have potential implications in whole energy metabolism in this disorder.

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Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 118.13/C28

Topic: A.07. Developmental Disorders

Support: NEOMED Bridge Funding to YL, and NIH/NIDCD DC-013074 to YW.

Title: Neuromodulation of inhibitory transmission by group I mGluRs in mouse MNTB neurons

Authors: R. J. CURRY[1,2], Y. WANG[3], *Y. LU[1,2]
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Abstract: The medial nucleus of the trapezoid body (MNTB) provides synaptic inhibition to many auditory brainstem nuclei and thus contributes to information processing in these auditory centers. MNTB also receives inhibitory inputs. However, not much is understood of the inhibition the MNTB itself receives and it remains entirely unknown how this inhibition is regulated. Here, we investigated group I metabotropic glutamate receptor (mGluR I, consisting of two members, mGluR1 and mGluR5) modulation of the glycinergic and GABAergic inputs to MNTB neurons in both wildtype (WT) mice and a fragile X syndrome (FXS) mouse model, in which the fragile X mental retardation gene 1 is knocked out (*Fmr1* KO). Loss of the FMR protein results in exaggerated activity of mGluR I, allowing for comparisons of mGluR I function under normal and altered conditions. The KO and WT mice (with a background of C57BL/6J) were purchased from the Jackson Laboratory and bred at NEOMED. Brainstem slices (250 μm) were prepared from P14-P25 mice. Whole-cell voltage clamp was used to record spontaneous and electrically evoked IPSCs (sIPSC and eIPSC) in MNTB neurons at 35 °C. Glycinergic and GABAergic IPSCs were pharmacologically isolated with bath application of gabazine (10 μM) and strychnine (1 μM), respectively. Immunohistochemistry detected expression of mGluR5 in both neuronal and non-neuronal cells in the MNTB. Activation of group I mGluRs by 3,5-DHPG (200 μM) increased sIPSC frequency and amplitude in both WT and KO neurons in a voltage-gated sodium channel dependent fashion for glycinergic transmission, but did not modulate glycinergic eIPSCs. For GABAergic transmission, 3,5-DHPG did not increase sIPSC frequency or amplitude, but did suppress eIPSCs in WT neurons, which could be prevented by the application of a CBR1 antagonist, AM251 (5 μM). The effect of 3,5-DHPG on GABAergic eIPSCs was highly variable in the KO, which supports the notion of impaired GABAergic signaling in the FXS model. The differential modulation of sIPSC and

eIPSC suggests that there may be differences in the mechanisms responsible for spontaneous and evoked glycine release. Additionally, group I mGluRs differentially regulate glycinergic and GABAergic inputs to the MNTB.

Disclosures: R.J. Curry: None. **Y. Wang:** None. **Y. Lu:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

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Topic: A.07. Developmental Disorders

Support: Simons Foundation SFARI grant

Title: Large-conductance potassium (BK) channels as potential therapeutic targets in fragile X syndrome

Authors: *E. J. SAWYER[1], A. R. ZINGALE[1], L. SCRADER[1,2]
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Abstract: Fragile X syndrome (FXS) is the most common inherited intellectual disability in humans, and also the most common monogenic cause of autism spectrum (AS) symptoms. FXS is typically caused by the transcriptional silencing of the *FMR1* gene on the X chromosome, which codes for the fragile X mental retardation protein (FMRP), an mRNA-binding protein integral to synapse formation and function. Large-conductance potassium (BK) channels are part of the molecular machinery that regulates neuronal membrane potential following action potential propagation and synaptic transmission, and are themselves regulated by FMRP through an interaction between FMRP and the β-subunit of the BK channel. We have recently shown that BK channel activity is regulated in an activity-dependent manner, highlighting the importance of BK channels for synaptic remodeling. Mice that have had the *fmr1* gene silenced or removed are a commonly-used animal model of FXS. In *fmr1* knockout mice, BK channel hypoactivity is associated with neuron firing irregularities and aberrant synapse formation, and systemic activation of BK channels in these mice partially rescues AS-related symptoms. We hypothesized that medial prefrontal cortical (mPFC) infusion of the BK channel activator BMS-204352 would be sufficient to rescue AS-related executive function abnormalities commonly observed in *fmr1* knockout mice. Single-housed knockout mice treated with BMS and subjected to a behavioral battery displayed improved social recognition as measured by a 3-chamber social exposure test, yet displayed no changes in either anxiety or motor activity relative to saline-treated control knockouts. Group-housed knockouts treated with BMS also displayed improved social recognition compared to saline-treated controls, but did not display changes in compulsive

behavior as measured by a marble burying task. Future molecular and electrophysiological research will assess the role of BK channels in mPFC synaptic plasticity in *fmr1* knockout mice.

Disclosures: E.J. Sawyer: None. **A.R. Zingale:** None. **L. Scrader:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Title: Upregulation of glial markers in the FMR1-knockout human neuronal progenitor cells is reversed by LIM domain kinase 2 inhibition

Authors: N. SUNAMURA, S. IWASHITA, K. ENOMOTO, T. KADOSHIMA, A. OKAMOTO, *F. ISONO
ASUBIO PHARMA Co., Ltd., Kobe-Shi, Japan

Abstract: Fragile X syndrome (FXS) is caused by the epigenetic silencing of the *FMR1* gene during embryonic development with the consequent loss of the Fragile X mental retardation protein (FMRP) expression. The pathological mechanisms of FXS have been extensively studied using the *Fmr1* knockout mice model, and the findings underscore the critical roles for FMRP in proper development, maturation, and organization of the neural network. However, the equivalence of those observations in human nervous systems is unexplored, and molecular mechanisms underlying the dysfunctions in FXS are still largely uncertain.
We show that the expression of glial markers *GFAP* and *S100B* are markedly upregulated in the human iPSC-derived *FMR1*-deficient neuronal progenitor cells (NPCs) as well as in the *FMR1*-deficient human NPC line ReNCell-CX. In contrast, the transcription factors important for neuronal development such as *NEUROD1* and *NEUROG2* were downregulated. Furthermore, *in silico* analyses showed that LIM domain kinase (LIMK) 2 signaling pathway was upregulated, whereas LIMK1 and bone morphogenic protein receptor signaling pathways were downregulated, in human iPSC-derived *FMR1*-deficient NPCs. Interestingly, aberrant gene expressions in both NPCs were rescued by treatment of LIMK2 inhibitor LX7101, although the LIMK1/2 dual inhibitor LIMKi-3 which could suppress synaptic abnormalities through inhibiting the actin depolymerizing factor cofilin in *Fmr1* knockout mouse had no such effect. Our findings support the previous observations that the functional deficiency of FMRP could cause abnormal gene expressions during nervous system development, and further suggest that LIMK1 and LIMK2 are differently associated with the downstream of FMRP. Inhibition of LIMK2 may become a novel approach for the treatment of FXS.

Disclosures: **N. Sunamura:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA CO., LTD. **S. Iwashita:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA CO., LTD. **K. Enomoto:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA Co., Ltd. **T. Kadoshima:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA Co., Ltd. **A. Okamoto:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA Co., Ltd. **F. Isono:** A. Employment/Salary (full or part-time):; ASUBIO PHARMA CO., LTD..

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: MU Committee for Faculty Research Grant

MU CAS Dean's Scholar Award

MU Undergraduate Scholar Award

MU Biology Department

Title: Examining the impact of Fragile X Mental Retardation Protein on adult neurogenesis in a novel insect disease model

Authors: *M. SORRELL, C. WORNER, K. A. KILLIAN
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Abstract: Fragile X syndrome (FXS), a form of inherited mental disability, results from a mutation in the regulatory region of the fragile X mental retardation 1 (*fmr1*) gene. This mutation leads to an increase in the number of CGG repeats, expanding the gene and resulting in hyper-methylation, transcriptional silencing, and loss of the gene product Fragile X Mental Retardation Protein (FMRP). FMRP is important for the regulation of mRNAs involved in synapse growth and function; its inhibition leads to increased protein synthesis within synapses. Mutations in *fmr1* also impact the function of adult neural stem cells (NSC), causing decreased hippocampal neurogenesis and learning deficits in adult mice. Our goal was to determine how FMRP regulates adult neurogenesis using a simple model, the cricket *Acheta domesticus*. We hypothesized that inhibition of FMRP would induce structural changes within the adult neurogenic niche and lead to a decrease in neurogenesis. We first used RNA-Seq to assemble the cricket transcriptome and identify the *fmr1* gene sequence in *A. domesticus*. *Ad'fmr1* was found to be highly conserved with 76% and 99% sequence similarity to the fruit fly *D. melanogaster* and cricket *Gryllus bimaculatus*, respectively. *In-situ* hybridization revealed intense expression of *Ad'fmr1* in the neurogenic niches of the adult cricket brain, and we used RNA interference (RNAi) to create a

loss-of-function phenotype in adult male and female crickets. On the first day of adulthood, crickets were given a 2µl injection of *fmr1* dsRNA. Animals were then sacrificed at different times post-injection (n=6 at each time point) and the optimal concentration for effective knockdown (KD), and duration of KD, was determined. RNAi effectiveness was validated using qPCR. Two days after injection of 2.5µg of *fmr1* dsRNA, *fmr1* transcript levels in adult male brains were not significantly different from control crickets injected with 2.5µg of DsRed2 dsRNA (DsRed2 is a coral gene not found in insects). However, by 8d post-injection (dpi) transcript levels were decreased by 47% and transcript levels continued to decrease with time, such that by 29dpi males exhibited a 78% decrease in gene expression. In contrast, the effect of the KD occurred more quickly in females, with *fmr1* transcript levels reduced by 75% as early as 2dpi. As in males, RNAi produced a long-term decrease in *fmr1* expression in the female brain, with *fmr1* expression levels reduced by 83% at 29dpi. We are currently examining the impact this inhibition of *fmr1* expression has on the structure of the neurogenic niche in order to provide insight into FMRP's role in neural stem cell function and neurogenesis in the adult brain.

Disclosures: M. Sorrell: None. **C. Worner:** None. **K.A. Killian:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Program#/Poster#: 118.17/C32

Topic: A.07. Developmental Disorders

Title: Morphological changes of hippocampal CA1 pyramidal neurons in Fragile X mice during development

Authors: *N. N. UMAR[1], *N. N. UMAR[1], T. G. BANKE[2]
[1]Aarhus Univ. Hosp., Aarhus C, Denmark; [2]Dept. of Biomedicine, Inst. of Physiol., Aarhus, Denmark

Abstract: Fragile X syndrome (FXS) belongs to a broad range of Autism Spectrum Disorders (ASDs) and occurs in approximately 1/4000 males and 1/8000 females. It is the most frequent cause of inheritable mental retardation and is due to an increase in the number of trinucleotide CGG repeats in the FMR1 gene leading to transcriptional silencing. FMR1 encodes the fragile X mental retardation protein (FMRP). FMRP is highly expressed throughout the brain, including in the hippocampus at dendritic spines, the major site of synaptic transmission. FMRP binds various cell mRNAs and functions as a translational repressor. The dendritic morphology in FXS patients is significantly impaired, with dendrites appearing long, thin and tortuous with a decrease in total synaptic area and receptors, resembling immature spine precursors, filopodia. This is thought to be one of the causes underlying the neuropsychiatric phenotypes seen in FXS patients. The Fmr1 KO mouse, a rodent model of FXS, exhibits many of the same traits as seen

in FXS patients, including spine abnormalities. Here we have investigated the developmental profile of Golgi stained CA1 pyramidal neurons in four different postnatal groups (P15-20, P30-40, P60-80 and P120-140) of Fmr1 KO mice and compared them with C57BL/6 WT mice. We have studied apical and basal dendrite trees using Scholl analysis, spine density as well as several other different spine morphological parameters. Preliminary analysis of our data suggests that Fmr1 KO neurons have less branching in both the apical and basal dendritic tree, except in the early groups (P15-20 and P30-40) where no clear differences were observed between WT and KO in the number of apical branching. Next, the differences in spine density were largest at earlier development time points (P15-20 and P30-40) with a ~20% reduction in KO. At >P30-40 no clear differences in density between apical KO and WT spines were observed. At P15-20, KO spines were slightly longer (7%) than WT. At P30-40, no difference in spine length was found. At >P30-40, KO spine length was shorter (12-20%) than WT. Interestingly, apical KO spine heads were smaller at all developmental stages (6-36%) as also reflected in a reduction in the total spine volume in the KO, which likely corresponds to an overall shrinkage of KO spines. Our data suggest that there are strong developmental abnormalities in dendritic branching, spine density, and spine shape between Fmr1 and WT mice in hippocampus with strong deficits in the Fmr1 KO mouse.

Disclosures: **N.N. Umar:** None. **T.G. Banke:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: NIH Grant MH100510

NIH Training Grant 5T32DA018926

Title: Impaired long-term plasticity of temporoammonic inputs to hippocampal CA1 neurons in a mouse model of Fragile X syndrome

Authors: *G. ORDEMANN[1,2,3], D. H. BRAGER[1,2]
[1]The Univ. of Texas At Austin, Austin, TX; [2]Ctr. for Learning and Memory, [3]Inst. for Neurosci. Grad. Program, Univ. of Texas at Austin, Austin, TX

Abstract: Fragile X syndrome (FXS) is the leading monogenetic cause of autism and intellectual disability. Dendritic dysfunction and changes in voltage-gated ion channels are rapidly expanding areas of research in FXS. We previously showed that the functional expression of h-channels (I_h) is higher in CA1 pyramidal neuron dendrites of the *fmr1-/y* mouse model of FXS

(Brager et al., 2012). Dendritic I_h plays a critical role in controlling long-term potentiation of temporoammonic inputs (TA-LTP) by limiting both synaptic integration and the duration of dendritic calcium plateaus. We hypothesized that the elevated dendritic I_h in *fmr1-/y* CA1 pyramidal neurons will thus reduce TA-LTP. We used whole-cell current clamp to record EPSPs before and after theta-burst stimulation of TA inputs. There was no significant difference in either paired-pulse ratio or input-output relationship between wildtype and *fmr1-/y* neurons either during baseline or after TBS. TBS significantly potentiated TA EPSP slope in wildtype (430±193%) but not *fmr1-/y* slices (109±45%). The total amount of depolarization and the number of spikes fired during TBS was significantly greater for wildtype neurons compared to *fmr1-/y* neurons. To test the impact of higher dendritic I_h, we repeated the TBS-LTP experiments in *fmr1-/y* neurons with h-channels blocked by intracellular application of ZD7288. Although the amount of depolarization during TBS was significantly greater with I_h blocked, TA-LTP was still significantly smaller than wildtype TBS-LTP. Our results suggest that long-term potentiation of temporoammonic inputs to CA1 pyramidal neurons is impaired in FXS. Further study of the mechanism underlying the impairment of TA-LTP in *fmr1-/y* CA1 neurons will utilize dendritic recordings and calcium imaging. The lack of TA-LTP in *fmr1-/y* CA1 neurons may contribute to hippocampal circuit dysfunction in FXS.

Disclosures: G. Ordemann: None. **D.H. Brager:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Dept of Biotechnology, Government of India

Title: The de novo proteome in FXS reveals multi-tiered flaws in homeostatic and mGlur-stimulated translation

Authors: *H. L. BOWLING[1], A. BHATTACHARYA[4], G. ZHANG[5], D. A. ALAM[2], J. Z. LEBOWITZ[2], S. ARYAL[2], S. GHOSH-DASTIDAR[6], N. BOHM-LEVINE[7], D. LIN[1], P. ANAND[6], R. PUCKETT[2], L. ZHOU[8], K. SHARP[8], R. S. MUDDASHETTY[9], K.

KIRSHENBAUM[3], E. BERRY-KRAVIS[8], T. A. NEUBERT[10], E. KLANN[11]
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Abstract: The current hypothesis for fragile x syndrome (FXS) pathology is that the loss of fragile X mental retardation protein (FMRP) results in the improper trafficking of normal FMRP targets leading to inappropriate translation in response to synaptic activity. However, due to technical limitations, there has been limited exploration of which transcripts are *de novo* translated following synaptic activity and in steady state, homeostatic conditions. To address this problem, we measured the *de novo* proteome in adult FXS model mouse hippocampal slices and compared it to that of wild-type littermates at both steady state and in response to mGluR-stimulation. Surprisingly, we noted divergent profiles for homeostatic and activity-dependent protein synthesis with few known FMRP targets being differentially translated. We noted that in contrast to the normal translational response to mGluR-stimulation, the *de novo* proteomic profile in FXS slices was disorganized proteomic. In addition, we analyzed the *de novo* candidates for a consensus in mRNA length, GC content, G-quadruplexes, and miRNA binding sites and found some trends consistent with previous reports, but no unifying characteristics. We confirmed our top candidates using multiple levels of validation and report differences in *de novo* synthesis versus accumulation of total protein for some targets, which informs the interpretation of protein expression studies in FXS. These findings suggest that FXS pathology is not solely due to the loss of translation of FMRP targets and disrupted activity-dependent protein synthesis, but also involves the aberrant synthesis of many previously undescribed targets in both homeostatic and activity-dependent conditions. To establish the relevance of these proteomic changes to human tissue, we examined three protein candidates in human patient plasma and found alterations in abundance in two proteins compared to healthy controls. One of these candidates was also rescued in FXS mouse blood by treatment with a S6K1 inhibitor, which previously was shown to ameliorate FXS phenotypes. In summary, our data suggest that the current understanding of translation changes underlying FXS are incomplete and that proteomic profiling may be useful in future biomarker efforts.

Disclosures: **H.L. Bowling:** A. Employment/Salary (full or part-time):; Torch Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Torch Biosciences, Inc. **A. Bhattacharya:** A. Employment/Salary (full or part-time):; Torch Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Torch Biosciences, Inc. **G. Zhang:** None. **D.A. Alam:** None. **J.Z. Lebowitz:** None. **S. Aryal:** None. **S. Ghosh-Dastidar:** None. **N. Bohm-Levine:** None. **D. Lin:** None. **P. Anand:** None. **R. Puckett:** None. **L. Zhou:** None. **K. Sharp:** None. **R.S. Muddashetty:** None. **K. Kirshenbaum:** None. **E. Berry-Kravis:** None. **T.A. Neubert:** None. **E. Klann:** E. Ownership

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Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: Brain Canada

Azrieli Neurodevelopmental Research Program

Title: Purinergic signaling in the cortex is significantly altered in the Fragile X syndrome model

Authors: A. L. SCOTT[1], A. POXON[1], C. R. WONG[2], A. CHEN[2], *L. C. DOERING[2]
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Abstract: Neural communication and the intricate choreography of signals required for the formation and preservation of neural connections is heavily dependent on reciprocal neuronal and glial interactions. Astrocytes are key participants in neurodevelopmental processes and defects to astrocyte signaling are implicated in many disorders, such as Fragile X Syndrome (FXS). In FXS, the loss of the Fragile X mental retardation protein (FMRP) expression from astrocytes is associated with improper synapse formation. These findings emphasize the importance of astrocyte-derived signals to the establishment and maintenance of neuronal connections.

During development astrocytes release a wide range of gliotransmitters and ATP is one of the predominant means of communication between astrocytes and neurons within the CNS. ATP is a fast, excitatory neurotransmitter known to act on astrocytes, modulate glio-neuronal transmission, and in this way regulate synaptic function. Given the integral role of ATP and its various metabolites to the regulation of synaptic development and function, we compared the physiological responses of astrocytes isolated from either postnatal wild-type ($FMRP^{+/+}$) mice or from transgenic *fmr1* knockout ($FMRP^{-/-}$) mice to exogenous purinergic stimulation.

The quantitative analysis of intracellular calcium levels revealed a significantly greater flux of intracellular calcium in $FMRP^{-/-}$ astrocytes in response to ATP (and UTP) in comparison to $FMRP^{+/+}$ astrocytes. Interestingly, blockade of several P2 receptors with suramin returned abnormal astrocytic calcium flux to wild-type levels. In addition, protein analysis demonstrated greater expression of several purinergic receptors belonging to the P2Y family in $FMRP^{-/-}$ astrocytes over the wild-type counterparts. Furthermore, enhanced expression of P2X7, an ionotropic channel responsive to ATP, was evident in $FMRP^{-/-}$ neurons. The differential expression of purinergic receptors may underlie the enhanced sensitivity of both $FMRP^{-/-}$

astrocytes and neurons, leading to atypical neural communication. Future analysis of the effects on astrocyte-neuron purinergic signaling in the $FMRP^{-/-}$ model will help elucidate the role these signals play in synapse function and the therapeutic relevance to FXS.

Disclosures: A.L. Scott: None. **A. Poxon:** None. **C.R. Wong:** None. **A. Chen:** None. **L.C. Doering:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Topic: A.07. Developmental Disorders

Support: Brain Canada

Azrieli Neurodevelopmental Research Program

Canadian Institutes of Health Research Doctoral Award (CIHR CGS-D)

Title: Alterations in astrocyte thrombospondin-1 expression in Fragile X syndrome

Authors: *K. E. REYNOLDS[1], A. L. SCOTT[2], L. C. DOERING[2]
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Abstract: The neurological symptoms of Fragile X syndrome (FXS) largely arise due to altered communication at tripartite synapses. At the tripartite synapse, astrocytes act as gatekeepers of brain function by secreting proteins which ensure robust and accurate neuronal signaling. One such astrocyte-secreted protein is thrombospondin-1 (TSP-1). In FXS, loss of FMRP in the developing brain decreases both TSP-1 production and secretion, impairing the structure and density of hippocampal dendritic spines as well as the formation of immature excitatory synapses, and thus clearly demonstrating TSP-1's importance to neuronal signaling. Both the production and secretion of TSP-1 are regulated through ATP- or UTP-induced activation of purinergic P2Y receptors, specifically P2Y4. However, the impact of purinergic signaling on TSP-1 expression remains unstudied in the context of FXS, or more broadly, Autism Spectrum Disorder. Adjusting the concentration of UTP *in vitro* sheds light on the ability of *Fmr1* knockout astrocytes to regulate TSP-1 expression, and by extension, to form immature synapses. We therefore isolated astrocytes from postnatal transgenic *Fmr1* knockout ($FMRP^{-/-}$) and control wildtype ($FMRP^{+/+}$) mice, and investigated their response to exogenous UTP stimulation *in vitro*. Both knockout and wildtype astrocytes demonstrated striking intracellular expression of TSP-1 following UTP treatment. This suggests that a failure in endogenous astrocyte activation could underlie the TSP-1 deficit seen in FXS, an impairment which we hypothesize is mediated

through the P2Y4 receptor. Future directions therefore include the use of agonists and antagonists to the P2Y4 receptor *in vitro* during UTP treatment, to further investigate this receptor's modulation of UTP-driven TSP-1 production in FMRP$^{-/-}$ astrocytes. P2Y4 receptor activity will also be correlated with the TSP-1-mediated synaptic rescue effect previously reported by our lab following TSP-1 treatment of *Fmr1* knockout astrocyte/wildtype neuron co-cultures. By further investigating the molecular mechanisms underlying TSP-1 expression at the FXS tripartite synapse, we can begin to elucidate the potential therapeutic relevance of this protein to FXS.

Disclosures: K.E. Reynolds: None. **A.L. Scott:** None. **L.C. Doering:** None.

Poster

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Azrieli Neurodevelopmental Research Program

Title: Activation of tenascin C and IL-6 in fragile X syndrome

Authors: *V. KRASOVSKA, L. C. DOERING
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Abstract: Tenascin C (TNC), a secreted extra-cellular matrix glycoprotein, is known to contribute to cell migration, axonal guidance, and synaptic plasticity. In the adult CNS, its expression remains high during neurogenesis. TNC also functions as a damage associated molecular patterns molecule (DAMP), through toll-like receptor 4 (TLR4) interaction. TLR4 activation by lipopolysaccharides (LPS) or TNC has been shown to induce pro-inflammatory cytokine production, stimulating interleukin-6 (IL-6). In FXS, plasma IL-6 levels are dysregulated, and in turn modulate responses associated with neurodevelopment. Impaired cell adhesion, migration, and excessive formation of excitatory synapses caused by elevated IL-6 levels may contribute to the altered cellular mechanisms of FXS. Thus, elevated levels of TNC may be responsible for the dysregulation of interleukin-6 through TLR4 activation, promoting excitatory synaptogenesis.
TNC, TLR4, and IL-6 expression were measured in the postnatal *FMR1* KO mouse model of FXS at postnatal (P) day 1, 7, 14, and 21. A significant increase of TNC and IL-6 expression was determined at P7, P14, and P21. No significant changes were seen in the expression of TLR4. Immunocytochemistry confirmed the expression and spatial distribution of the three targets *in*

vitro in primary astrocyte cultures. Since FXS is linked to functional changes in neural circuitry associated with an imbalance of excitatory and inhibitory synapses, activation of the TLR4 with LPS and exogenous TNC will be performed to determine if IL-6 will effect the formation of excitatory synapses.
Completion of this research will be the first to determine a role for TNC in FXS, in terms of activating TLR4 and inducing pro-inflammatory cytokines. By assessing the cellular mechanisms involved in the activation of an inflammatory response, potentially through TNC, a novel therapeutic option could be made available to target inflammation in FXS.

Disclosures: V. Krasovska: None. **L.C. Doering:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

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Support: Brain Canada

Azrieli Neurodevelopmental Research Program

Title: Altered poly(ADP-ribose) polymerase-1 levels in Fragile X syndrome

Authors: *S. S. JHALA
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Abstract: Fragile X syndrome (FXS) is an inherited form of intellectual disability and a leading cause of autism. The underlying pathophysiological feature of FXS involves loss of the FMRP protein due to *fmr1* gene silencing leading to enhanced glutamatergic signaling, synaptic dysfunction, oxidative stress and mitochondrial dysfunction. However, the biochemical signaling pathways involved in the altered cellular signaling in FXS are mostly unknown. In this study, we studied a role of the poly (ADP) ribose dependent mechanism in the Fragile X knockout mouse model and in primary astrocyte cultures obtained from $FMRP^{-/-}$ mice. Poly (ADP) ribose polymerase-1 (PARP-1), an important enzyme of poly(ADP)-ribosylation with a key role in the regulation of transcription and the development of excitotoxicity is associated with the pathogenesis of various disorders of the CNS. Immunoblot analysis of PARP-1 protein levels in vivo from $FMRP^{-/-}$ mice and in vitro with primary cortical astrocytes showed PARP-1 cleaved products. A significant increase in the levels of 89kDa protein fragments was observed at postnatal day-7 and -14 in the hippocampus and the cortex. However, no significant change was observed at postnatal day 21 in both the hippocampus and cortex. Analysis of $FMRP^{-/-}$ primary astrocytes culture showed a significant increase in 89kDa PARP-1 cleaved fragments as compare

to the wild type astrocytes. Our findings suggest that PARP-1 activation and cleavage is an important event in the pathology of FXS and may be involved in FMRP dependent downregulation of glutamate receptors and transporters in the pathophysiology of FXS.

Disclosures: S.S. Jhala: None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 118.24/C39

Topic: A.07. Developmental Disorders

Support: University of Illinois at Urbana-Champaign (N-P.T.)

NARSAD Young Investigator Award (N-P.T.)

Title: Mdm2 mediates FMRP- and Gp1 mGluR-induced protein translation and neural network activity

Authors: *D.-C. LIU[1], J. SEIMETZ[2], A. KALSOTRA[3,4], N.-P. TSAI[5]
[1]Neurosci., [2]Biochem., Univ. of Illinois Urbana-Champaign, Urbana, IL; [3]Biochem., 3Department of Biochemistry, Sch. of Mol. and Cell. Biology, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [4]Carl R.Woese Inst. of Genomic Biology, Univ. of Illinois, Champaign, IL; [5]Mol. and Integrative Physiol., 1Department of Mol. and Integrative Physiology, Sch. of Mol. and Cell. Biology, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Activating Group 1 metabotropic glutamate receptors elicits multiple translation-dependent neural plasticity mechanisms that are crucial to animal behavior and circuit development. Dysregulated Gp1 mGluR signaling has been observed in numerous neurological and psychiatric disorders. In this study, we identified a novel mechanism through which Gp1 mGluR mediates protein translation and neural plasticity. Using a multi-electrode array (MEA) recording system, we showed that activating Gp1 mGluR elevates spontaneous spike frequency and burst activity. Importantly, we validated that elevating neural network activity requires protein translation and is dependent on fragile X mental retardation protein (FMRP). In an effort to determine the mechanism by which FMRP mediates protein translation and neural network activity, we demonstrated that a ubiquitin E3 ligase, murine double minute-2 (Mdm2), is required for Gp1 mGluR-induced translation and neural network activity. We found that Mdm2 acts as a translation suppressor, and FMRP mediates its ubiquitination and degradation upon Gp1 mGluR activation. These data revealed a novel mechanism by which Gp1 mGluR and FMRP mediate protein translation and neural network activity, potentially through de-repressing Mdm2. Our results introduce an alternative way for understanding altered protein translation and brain

circuit excitability associated with Gp1 mGluR in neurological diseases such as fragile X syndrome (FXS).

Disclosures: D. Liu: None. **J. Seimetz:** None. **A. Kalsotra:** None. **N. Tsai:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

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Topic: A.07. Developmental Disorders

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NIH/NICHD R01HD083181

The Stedman West Foundation

Texas Children's Hospital

Title: Loss and restoration of Fmr1 in component cell types of neural microcircuits reveals distinct requirements for FMRP in the developing nervous system

Authors: *D. CONNOLLY[1,3], S. SORIANO[1,3], C. M. MCGRAW[4], B. E. O'NEILL[5], H. L. VANDERPOOL[6], A. CHAHROUR[1], A. J. LIANG[1,3], B. P. VICARI[2,3], S. VEERARAGAVAN[1,3], C. S. WARD[1,3], D. L. NELSON[1,3], R. C. SAMACO[1,3]
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Abstract: Behavior is governed by both genetic and environmental factors, yet the genetic basis for normal behavior remains poorly explored in spite of a need to better understand it for human health. Given that single gene alterations account for features present among multiple neurodevelopmental disorders, genetic rodent models with high construct validity provide the opportunity to experimentally test and evaluate how these genes contribute to aspects of behavior such as sociability and memory in both healthy and disease states. One example of a monogenic neurodevelopmental disorder that has shaped our understanding of behavior in this context is Fragile X syndrome (FXS). FXS is caused by trinucleotide repeat expansions in *FMR1* encoding FMRP and accounts for one of the leading forms of inherited intellectual disability. Co-occurring behavioral conditions such as autism, anxiety and hyperactivity are also highly prevalent. The

Fmr1 rodent models have played a key role in delineating the relationship between FMRP deficiency and behavioral features; however, the less than favorable outcomes in recent clinical trials for FXS clearly highlight the complexities concerning its pathophysiology. Moreover, these results have brought the field to a crossroads with respect to current animal models of FXS, underscoring the need to understand how best to leverage these tools for studies of actionable translational relevance. Here, we set out to test the hypothesis that features of FXS may be differentially sensitive to the spatio-temporal function of FMRP as one possible explanation for some of the discordance observed in studies of FXS individuals in comparison with animal models of the disorder. To this end, we first identified reproducible neurobehavioral phenotypes in an *Fmr1* mouse model, replicating previously reported alterations in anxiety-like behavior, spontaneous exploratory activity, sensorimotor gating and some aspects of learning and memory. We then compared the neurobehavioral outcomes in mice selectively lacking FMRP in either excitatory or inhibitory neurons of the brain, and tested whether these features can be normalized upon genetic restoration either in early development or during adulthood. Taken together, our work identifies a novel conceptual paradigm for FXS, suggesting the presence of both developmental and non-developmental features that occur due to FMRP deficiency in distinct neural cell types. These findings are also highly instructive, yielding insight into therapeutic windows of intervention with respect to lifespan that may need to be specifically targeted for improved outcomes in the treatment of FXS.

Disclosures: D. Connolly: None. **S. Soriano:** None. **C.M. McGraw:** None. **B.E. O'Neill:** None. **H.L. Vanderpool:** None. **A. Chahrour:** None. **A.J. Liang:** None. **B.P. Vicari:** None. **S. Veeraragavan:** None. **C.S. Ward:** None. **D.L. Nelson:** None. **R.C. Samaco:** None.

Poster

118. Fragile X: Mechanisms of Pathophysiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 118.26/C41

Topic: A.07. Developmental Disorders

Support: NIMH MH103455

Title: The effect of genetic interactions between Cyfip1 and Fmr1 on synaptic and behavioral phenotypes

Authors: G. BARBAYANNIS[1], S. ABDELMAGED[1], T. KUMAR[1], A. KAMALI TAFRESHI[1], K. L. SZABLA[2], D. L. BENSON[2], *O. BOZDAGI[1]
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Abstract: CYFIP1 is a binding partner of FMRP, and *CYFIP1* has been proposed as a risk gene for several neuropsychiatric disorders, which are characterized by cognitive, social, and emotional dysfunction. Mice with a loss-of-function mutation of the Cyfip1 gene (*Cyfip1*$^{+/-}$) have a synaptic phenotype similar to *Fmr1*$^{-/y}$ mice. To examine whether mutations causing CYFIP1 and FMRP deficiency interact on common molecular targets, which may affect behavioral phenotypes, we crossed *Cyfip1*$^{+/-}$ and *Fmr1*$^{-/y}$ mice. Individual and crossed mutants (3 weeks old) show an exaggerated mGluR-LTD phenotype that was significantly different from wild type mice and similar between all mutants supporting the use of a shared mechanism. We next tested *Cyfip1*$^{+/-}$ */Fmr1*$^{-/y}$ double mutant mice for additional synaptic phenotypes that could arise as a consequence of genetic interaction. Double mutant mice showed no differences in paired pulse facilitation, but showed significantly diminished LTP (induced by a single 100 Hz stimulation) and displayed decreased NMDA receptor-dependent LTD (induced by low frequency stimulation), phenotypes that are not seen in either single mutant. To test for social deficits that are relevant to autism, we are using a sociability test that has proven to be robust in mice. All four genotypes (*Cyfip1*$^{+/-}$, *Fmr1*$^{-/y}$, *Cyfip1*$^{+/-}$ */Fmr1*$^{-/y}$ double mutant, and wild type) are being examined in the three-chamber social interaction test. Preliminary data suggest that *Cyfip1+/-/Fmr1-/y* double mutant mice show reduced social interaction behaviors when exposed to a novel mouse, compared to single mutant *Cyfip1+/-* or wild type mice, which displayed robust social exploration, sociability, and preference for a stranger novel mouse. Our data support that CYFIP1 shares some roles with FMRP, but has an interactive effect with FMRP in the regulation of postsynaptic function in mature synapses and suggest a means by which altered levels of CYFIP1 could increase disease severity.

Disclosures: G. Barbayannis: None. **S. Abdelmaged:** None. **T. Kumar:** None. **A. Kamali Tafreshi:** None. **K.L. Szabla:** None. **D.L. Benson:** None. **O. Bozdagi:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.01/C42

Topic: A.07. Developmental Disorders

Support: NSERC-PGSD

Title: Neuroanatomical correlates of social behaviour

Authors: *D. J. FERNANDES[1], L. QIU[2], J. P. LERCH[3]
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Abstract: Social behaviour is an important function of the brains of humans and mice. However, the neurological basis of natural and longitudinal social interactions are poorly known. While mouse studies have been useful in understanding this relationship, social behaviour is typically quantified in artificial paradigms over short-timescales. Using a combination of video and Radio Frequency ID (RFID) tracking, we tracked and phenotyped several groups of individually-identifiable mice in standard laboratory housing. RFIDdata was analyzed using models from statistical physics and information theory to calculate social and non-social behaviour metrics. Fast semi-automatic quantificationof video data was used for validation. Our behavioural measures captured knownsocialibity differences in the BTBR andC57BL6/J mouse strain. BTBR mice were on average further apart from their cagemates than C57BL6/J mice and C57BL6/J mouse positions are highly influenced by their neighbours. C57BL6/J mice were monitored simultaneously over several weeks, through the development periods of puberty and early adulthood. In conjunction, Manganese-Enhanced MRI was used to obtain longitudinal in-vivo neuroanatomy over this observation period. We found that the size of cerebellar, hippocampal, and frontal cortical regions are significantly associated with mouse social behaviour. Furthermore,cerebellar and frontal cortical volumes in neonatal life are associated with social behaviour post-puberty. By tracking individually-identifiable mouse positions and measuring longitudinal neuroanatomy, were able to identify neuroanatomical structures that correlate with social behaviours.

Disclosures: **D.J. Fernandes:** None. **L. Qiu:** None. **J.P. Lerch:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Topic: A.07. Developmental Disorders

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BRAINS for autism foundation

Ed and Sue Rose Distinguished Professorship

The Hartwell Foundation

Debra Caudy and Clay Heighten

Title: Stiatal ablation of Neuroligin-1 affects motor learning/memory and expeditious decision-making

Authors: *F. ESPINOSA[1], I. FILONOVA[1], C. M. POWELL[2]
[1]Neurol. and Neurotherapeutics, [2]Neurol. and Neurotherapeutics, Dept. of Psychiatry and Neurosci. Grad. Program, U.T. Southwestern Med. Ctr., Dallas, TX

Abstract: Neuroligin-1 (NLGN1) is a postsynaptic protein involved in synapse specification and maintenance in an activity-dependent manner. NLGN1 function may shape brain circuitry in part by modulating synaptic function through the local stabilization of NMDA receptor clusters. Active synapses where NLGN1 is expressed may be more stable than inactive synapses and those not expressing it. Furthermore, genetic studies in humans show that mutations in *NLGN1* could be involved in the pathology of autism spectrum disorders (ASD). Knockout mice constitutively deficient in NLGN1 present phenotypes in the repetitive/restricted interests and social domains considered relevant to ASD. To further test the importance of this protein in some of these phenotypes, we knocked down *Nlgn1* by Adeno-associated virus-driven expression of a known *Nlgn1*-specific microRNA. Large areas in the dorsal and ventral striatum, active during grooming behavior, were specifically targeted. Surprisingly, in contrast to mice where *Nlgn1* was depleted from birth, knockdown of *Nlgn1* in these brain regions in the adult mouse does not increase grooming but may affect motor memory as seen in the rotarod. Besides its function in motor control, the striatum is now believed to also modulate cognitive functions. In our experiments, adult Nlgn1 knockdown also affected expeditious decision-making as seen in a cued choice water maze task and in a reversal test in the “water” version of the Y maze. In these tasks, speed of decision-making was significantly reduced after knockdown of Nlgn1, a phenotype that was exacerbated upon contingency changes. Our findings seem to support recent literature suggesting that the dorsal striatum is involved in selection and initiation of actions whereas the ventral striatum is thought to be where the value (the motivational/emotional component) of sensorimotor stimuli is integrated according to outcomes. Future experiments will differentiate between effects mediated by dorsal or ventral striatum and will examine associated changes in synaptic function using acute striatal slices.

Disclosures: F. Espinosa: None. **I. Filonova:** None. **C.M. Powell:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: A.07. Developmental Disorders

Support: KU Leuven grant - "Opening the Future"

FWO (Research Foundation Flanders) post-doctoral fellowship

Title: Social behavior deficits in a SPRED1 knockout mouse model of Legius syndrome

Authors: *S. C. BORRIE[1], E. PLASSCHAERT[1], Y. ELGERSMA[2], S. A. KUSHNER[2], E. LEGIUS[1], H. BREMS[1]
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Abstract: Legius syndrome is a Rasopathy disorder stemming from mutations in the *SPRED1* gene. SPRED1 is a member of the Sprouty/Spred1 family, which acts as a negative regulator of the RAS-MAPK pathway. Legius syndrome presents as a milder phenotype of Neurofibromatosis type 1, a well-characterized Rasopathy disorder stemming from mutations in neurofibromin. Common to these disorders are neurological problems including cognitive deficits and increased incidence of autism spectrum disorder (ASD) or ADHD. A *Spred1-/-* mouse model for Legius syndrome demonstrates spatial learning deficits, however it is not known whether this model also recapitulates other aspects of the disorder, such as ASD-like symptoms. To further study this phenomenon, we examined social behaviors in *Spred1-/-* and *Spred1+/-* mice, to ask if social deficits are observed in these models, and whether any observed deficits can be rescued. Both *Spred1-/-* and *Spred1+/-* mice displayed abnormal social behavior in the automated tube test. Other social behaviors were also impaired in *Spred1-/-* mice, including nesting, an intrinsic social behavior. Social deficits in *Spred1-/-* could be reversed in adult mice by inhibiting the RAS-MAPK pathway. Conditional knockout strategies have been used to explore the regional role of Spred1. These findings suggest that deficits in social behaviors that are core symptoms of Rasopathies can be reliably modelled in Spred1-/- mice, and that RAS-MAPK pathway overactivation underlies altered social behavior in this model.

Disclosures: S.C. Borrie: None. **E. Plasschaert:** None. **Y. Elgersma:** None. **S.A. Kushner:** None. **E. Legius:** None. **H. Brems:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.04/C45

Topic: A.07. Developmental Disorders

Support: Kenyon College Summer Science Scholars

Kenyon College Department of Neuroscience

Title: GABA A alpha 2 receptor subunit agonism improves sociability and object recognition memory in BTRT+ tf/J mice

Authors: S. NAGUIB[1], *H. G. MCFARLANE[2]
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with an unknown etiology, characterized by impairments in communication, social interaction deficits and repetitive, restricted behaviors. The inbred BTBR T^{+}tf/J (BTBR) mouse strain displays behaviors that are analogous to these cardinal traits of ASD. Specifically, compared to C57BL/6J (B6) controls they show poor social interactions, elevated repetitive self-grooming and memory deficits. Additionally, BTBR mice have been shown to have reduced GABAergic neurotransmission in comparison to B6 mice. Previous studies have demonstrated that social behavior in BTBR mice can be improved by concurrently agonizing both the $GABA_A$ α2 and α3 subunits. The $GABA_{A\alpha2}$ receptor subunits are heavily localized in the hippocampus (HP), striatum(STR) and the amygdala(AM) and when stimulated, have been shown to modulate anxiety and working memory. The aim of the present study was to determine whether agonism of the $GABA_{A\alpha2}$ receptor subunit is sufficient to improve social behavior and memory in adult (42-90 days old) male BTBR mice. Social approach behavior and object recognition memory were tested using the Three Chamber Social Approach test. Three groups of mice were tested: vehicle treated B6 controls, vehicle treated BTBRs and BTBRs treated with the selective $GABA_{A\alpha2}$ agonist TCS-1105. Testing began ten minutes after treatment. As expected, B6 mice showed a statically significant preference for the social environment over the non-social one and vehicle treated BTBRs showed a significant preference for the non-social environment. BTBR mice treated TCS-1105 showed a significant preference for the social environment, similar to B6 controls. TCS-1105 treated BTBR mice also showed a significant drop in self grooming behavior. In the object recognition test, the B6 mice and the treated BTBR mice spent significantly more time investigating the novel object, whereas the untreated BTBR mice showed no preference. Given the distribution of $GABA_{A\alpha2}$ subtypes in HP, STR and AM, it is possible that dopamine signaling plays a role in the improvement seen in BTBR memory and social behavior.

Disclosures: S. Naguib: None. **H.G. McFarlane:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.05/C46

Topic: A.07. Developmental Disorders

Support: ARC Discovery Grant (DP150102496)

Title: Sex differences in extinction of conditioned fear in juvenile rats

Authors: *C. PARK[1], D. E. GANELLA[2], J. H. KIM[3]
[1]The Florey Inst., Melbourne, Australia; [2]Florey Inst. of Neurosci. and Mental Hlth., Melbourne University, Australia; [3]The Florey Inst. of Neurosci. and Mental He, Parkville, Australia

Abstract: By 6 years of age, the prevalence of anxiety disorders is more than twice as high in female than male children. The present study explores sex differences in the relapse propensity, a core pathology of anxiety disorders, in juvenile (i.e. postnatal day 14-21) rats. All rats were fear conditioned with 3 white-noise - footshock pairings and extinguished with 60 white-noise presentations, on day 1 and 2. Experiment 1 investigated renewal of fear. Rats were tested with a 2-min white-noise presentation in either the extinction or a non-extinction context on day 3. Female rats tested in the non-extinction context showed significantly higher levels of freezing compared to those tested in the extinction context (i.e. displayed renewal), whereas male rats did not show renewal. Experiment 2 investigated reinstatement. Rats received either a mild reminder footshock or were merely exposed to the extinction chamber on day 3, and were tested with white-noise in the extinction context on day 4. At test, female rats from the reminder group showed significantly higher levels of freezing compared to the non-reminder group (i.e. displayed reinstatement). Male rats did not reinstate despite receiving a reminder shock. Experiment 3 investigated spontaneous recovery. Rats were tested in the extinction context either on day 3 or 7. Female rats tested on day 7 showed significantly higher freezing compared to those tested on day 3 (i.e. displayed spontaneous recovery). Male rats did not spontaneous recover, regardless of the test day. In summary, our findings indicate juvenile female rats demonstrated renewal, reinstatement and spontaneous recovery, which are readily observed in adult rodents. Additionally, these behaviours were not observed in juvenile male rats. Thus, juvenile female rats may be more behaviourally mature compared to juvenile male rats, possibly due to more adult-like neural circuitry underlying extinction learning.

Disclosures: C. Park: None. **D.E. Ganella:** None. **J.H. Kim:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.06/C47

Topic: A.07. Developmental Disorders

Title: Early postnatal treatment with valproic acid results in regression and perseveration

Authors: *S. A. NORTON, S. PAREKH, J. GIFFORD, A. W. KUSNECOV, G. C. WAGNER
Psychology, Rutgers Univ., Piscataway, NJ

Abstract: Prenatal exposure to valproic acid (VPA) has been linked to autism spectrum disorder (ASD) in humans. Therefore, prenatal VPA treatment in rodents has become an acceptable model of ASD. Specifically, prenatal VPA has been shown to induce social deficits, perseveration, and hyperserotonemia. In this study, *postnatal* VPA was tested for ASD-like behavioral and neurochemical deficits. Mice (C57BL/6) were treated on postnatal days 7 or 14 with 300 mg/kg (P7) or 400 mg/kg (P14) VPA. Treatment at either time caused regression (loss

of acquired skills) in age-appropriate tests of development. Further, treatment on P14 caused, in adult mice, perseveration and delayed reversal learning in a water Y maze task, while task acquisition was normal. Treatment on P14 also led to hippocampal, striatal, and cerebellar hyperserotonemia in adulthood. After either P7 or P14 VPA, no deficits in a social approach task, using the social chamber test (considered a measure of general sociability), were seen at P30 (adolescence) or P90 (adulthood). Future studies will determine if other measures of social interaction (e.g., social play or social contextual conditioning) reveal deficits in social interaction in mice treated on P7 or P14 with VPA. Nonetheless, it appears that VPA treatment on either P7 or P14 may be an effective model of autistic regression.

Disclosures: S.A. Norton: None. **S. Parekh:** None. **J. Gifford:** None. **A.W. Kusnecov:** None. **G.C. Wagner:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Program#/Poster#: 119.07/C48

Topic: A.07. Developmental Disorders

Support: NJ Governor's Council for Medical Research and Treatment of Autism grant

Rutgers University – Newark Chancellor's IMRT grant

Title: The effects of MPEP on learning, sensorimotor, and emotional behavior in Plexin-A3-deficient mice

Authors: T. S. TRAN[1], A. KOSC[2], S. PACELLI[3], S. YANG[1], *M. W. SHIFLETT[2]
[1]Biol. Sci., [2]Psychology, Rutgers Univ. Newark, Newark, NJ; [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The precise formation and refinement of synapses during development are important to the overall wiring of functional neural circuits in the adult animal. Thus, alterations in synaptic transmission affect neural activity that may ultimately impinge on behavior and mental function. Previously, we demonstrated that the class 3 semaphorin 3F (Sema3F) acting through Neuropilin 2/Plexin-A3 (Nrp2/PlxnA3) holoreceptor complex signals *in vivo* to restrain dendritic spine morphogenesis of cortical pyramidal neurons and hippocampal neurons during post-natal development. Loss of semaphorin signaling increases spine number, distribution, and excitatory synaptic transmission in these neurons. While members of the Semaphorin family and their receptors (Neuropilins and Plexins) have been implicated in the etiology of a number of neurodevelopmental disorders, including autism spectrum disorder, the effects on behavior and mental function of dysregulated semaphorin signaling have not been fully addressed. In this

study, we examined learning, sensorimotor, and emotional behavior in mice harboring a mutation of the *PlxnA3* gene. Additionally, we examined the effects of systemically-administered 2-Methyl-6-(phenylethynyl)pyridine (MPEP), a selective mGluR5 antagonist that reduces cellular excitability, in *PlxnA3* mutant animals' behavior compared to age-matched controls. Adult *PlxnA3* null mutants showed significant impairments in object recognition memory and preference for social novelty when compared with control mice. Furthermore, the mutant animals displayed impaired motor function in the rotarod test and showed excessive repetitive stereotypic grooming behavior. Our results demonstrated that MPEP has a significant effect in normalizing the grooming behavior of the *PlxnA3* mutants. Currently, we are performing additional behavioral tests such as the elevated zero maze and marble-burying test to examine anxiety in both mutant and control animals. Our results suggest that loss of *PlxnA3* may induce aberrant behaviors through increased excitatory synaptic transmission that is remediated, in part, by inhibiting mGluR5 function. Collectively, our studies will provide a better understanding of how changes in dendritic spine morphology and synaptic transmission at the cellular level influence complex behavior output in the animal.

Disclosures: T.S. Tran: None. **A. Kosc:** None. **S. Pacelli:** None. **S. Yang:** None. **M.W. Shiflett:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Topic: A.07. Developmental Disorders

Support: PICT-2013-1362

UBACYT2016-20020150100120BA

Title: Peers can rescue autism-related behaviours after prenatal exposure to valproic acid: Role of the piriform cortex

Authors: *A. M. DEPINO[1], M. CAMPOLONGO[2], N. KAZLAUSKAS[2], G. FALASCO[3], L. URRUTIA[3], N. SALGUEIRO[2]
[1]Inst. For Physiology, Mol. Biol. and Ne, Buenos Aires, Argentina; [2]Inst. For Physiology, Mol. Biol. and Neuroscience, UBA-CONICET, Buenos Aires, Argentina; [3]Lab. de Imágenes Preclínicas, Ctr. de Imágenes Moleculares, FLENII, Buenos Aires, Argentina

Abstract: Autism spectrum disorder is characterized by poor social interaction. Symptoms appear in early life and persist in adulthood. Early social stimulation can help revert some of the symptoms, but the biological mechanisms of action are unknown. Our aim was to analyze the

effects of early social stimulation on autism-related behavior in the mouse and its consequences on brain function. To this aim, we exposed mice to valproic acid (VPA) at gestational day 12.5. We show that these mice play less as juveniles and, when reared with other VPA mice, they perform less social interaction in adulthood. However, when VPA animals were caged with control animals between postnatal day (PD) 21 to PD60, this behavioral alteration was rescued. Interestingly, repetitive behaviors (time in self-grooming, and arm alternation in the Y-maze) and depression-related behaviors (immobility in tail suspension and forced swim tests) were not affected by this protocol of social enrichment. Moreover, anxiety related behaviors assayed in either the elevated plus maze, the open field, and the dark/light box were not affected by either the prenatal or the postnatal treatment. We then used [18F]-FDG preclinical PET imaging for an unbiased analysis of the whole brain of these mice, and found that VPA animals present high levels of metabolism in basal conditions, mainly in the piriform cortex (Pir), a region involved in social behavior in mice. Remarkably, this effect was reversed after social stimulation. In addition, we found increased dopamine turnover in the Pir in VPA-VPA mice, which is normalized in peer-rescued animals. Finallly, we evaluated the activation of the Pir in response to novel social stimuli, in all our experimental groups.

Disclosures: **A.M. Depino:** None. **M. Campolongo:** None. **N. Kazlauskas:** None. **G. Falasco:** None. **L. Urrutia:** None. **N. Salgueiro:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.09/C50

Topic: A.07. Developmental Disorders

Support: NHMRC Career Development Fellowship Grant APP1083309

Title: Role of dopamine 1 and dopamine 2 receptors across adolescence in addiction-related behaviours

Authors: *E. R. CULLITY, J. H. KIM, H. MADSEN
Florey Inst. of Neurosci. and Mental Hlth., Melbourne, Australia

Abstract: Adolescent abuse of methamphetamine (meth) is a significant social and public health concern worldwide, and a growing problem in Australia; however, few studies have investigated addiction in adolescence. Drugs of abuse trigger the activation of dopamine receptors in brain regions implicated in reward processing. My first aim is to investigate the developmental trajectory of dopamine receptor 1 (D1R) and 2 (D2R) expressing neurons in the striatum, amygdala and insula cortex across adolescence, starting from the juvenile period (postnatal day P17) to adulthood (P70). My second aim is to examine potential age differences in meth

conditioned place preference (CPP) in adolescent (P35) and adult (P70) D1R- and D2R-green fluorescent protein (GFP) mice and investigate the involvement of D1R and D2R expressing cells in these behaviours. I hypothesise that adolescents form stronger meth CPP compared to adults, which is associated with age differences in D1R- and/or D2R-expressing cells in discrete neural regions.
Preliminary stereology data showed that male dorsal striatum D1R cell population, D1R cell density, and volume do not change across adolescence (p's>0.05). Our meth CPP study observed that mice, irrespective of age, acquired meth CPP at doses of 0.1 and 0.3mg/kg (p's<0.001), but not 1 and 3mg/kg (p's>0.05). At the 3mg/kg dose, there was a weak trend for an adolescent propensity to form a preference versus aversion (p=0.1). Only mice that formed a preference to the 0.1 and 3mg/kg doses proceeded to extinction. Seven sessions of extinction reduced the meth CPP in adult compared to adolescent mice at 0.1mg/kg dose (p<0.05). Similar extinction did not reduce meth CPP with 3mg/kg meth (p>0.05), irrespective of age.
Taken together, results suggest male dorsal striatum volume and D1R cell population and density are similar across development and therefore unlikely to explain differences in meth CPP behaviours in adolescent compared to adult mice.

Disclosures: E.R. Cullity: None. **J.H. Kim:** None. **H. Madsen:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.10/C51

Topic: A.07. Developmental Disorders

Support: R21HD080498

OD011107

Title: A non-invasive eye tracking study using rhesus macaques

Authors: *T. MURAI[1,4], C. PHI[1], M. D. BAUMAN[1,2,3]
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Abstract: Visual information is one of the most important cues in social cognition for both humans and non-human primates (NHPs). Individuals diagnosed with neurodevelopmental or neuropsychiatric disorders, such as autism or schizophrenia, display aberrant gaze patterns toward social stimuli. Investigating the nature of gaze patterns of NHPs and comparing them with those in humans could help us understand etiology of and drug effects on the disorders. In

this study, social and nature videos (30 seconds long) were presented to two age-category rhesus monkeys and their gaze patterns were investigated using a non-invasive eye-tracking protocol. Six infant (one male and five females) and four juvenile (two males and two females) rhesus macaques were presented five social and five nature videos in each session. Each monkey performed six eye tracking sessions within 60 days with a minimum 3-day interval between sessions. The social videos included rhesus macaque social behaviors such as aggression, grooming, play, mounting, foraging or sitting in groups without overt social behavior (nonspecific social behavior videos). The nature videos depicted birds, insects/invertebrates, land mammals, marine mammals/fish and landscapes/flowers. Six different stimulus sets were prepared, and every animal saw the same stimulus set at each testing time point. Calibration and data acquisition succeeded in all sessions. It is noteworthy that none of the animals were trained or habituated prior to testing. In both age groups, monkeys looked at the social videos significantly longer than the nature ones. Interestingly, juveniles looked at each video longer than infants. These results suggest that rhesus monkeys recognize conspecifics and are attentive to their behaviors from an early age. In addition, attention to visual information appears to increase during the juvenile stage. In future studies, this non-invasive eye tracking method can be applied to monkeys with low-sociability, either spontaneous or drug-induced, and it can contribute to a better understanding of monkeys' visual processing of social cognition and development of novel treatments for neurodevelopmental and neuropsychiatric disorders. This study is funded by R21HD080498 and OD011107.

Disclosures: **T. Murai:** None. **C. Phi:** None. **M.D. Bauman:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.11/C52

Topic: A.07. Developmental Disorders

Support: Vassar College Internal Funds

Title: Distress vocalization deficit as an early postnatal marker of abnormal neurodevelopment in the fmr1 KO mouse model of autism

Authors: *B. ZUPAN[1], A. KASHNAVIS[2], M. MOROCHNIK[2]
[1]Psychology, [2]Psychological Sci., Vassar Col., Poughkeepsie, NY

Abstract: Fragile X syndrome (FXS) is a neurodevelopmental disorder caused by silencing of the fragile X mental retardation 1 gene (*FMR1*). It is the most common heritable cause of intellectual disability and the largest monogenic cause of autism with which it shares a number of symptoms including cognitive inflexibility and social anxiety. The *fmr1* knock-out (KO)

mouse recapitulates numerous symptoms of the condition including learning deficit, abnormal sociability and sensory hyperreactivity. Isolation-induced ultrasonic vocalization (USV) is a reliable measure of social communication in neonatal mice, and we have previously reported that both male and female *fmr1* deficient pups exhibit reduced frequency of USV during the first postnatal week relative to wild type (WT) pups. Specifically, while the number of USVs did not change in WT mice over time, KO pups showed reduced vocalizations at P4 and P8, but a significant increase at P12; data suggestive of delayed onset of distress-induced social communication in *fmr1* deficient pups. Abnormal pup vocalizations have been observed in a number of mouse models of neurodevelopmental disorders and, in human, reduced and delayed onset of infant vocalization has been linked with subsequent diagnoses of autism. However, reduced isolation-induced USVs in our model were accompanied by altered maternal care as measured by increased pup retrieval latency and duration, maternal behaviors which could influence pup vocalization patterns. To assess whether the delay in isolation-induced USV in KO pups was indicative of a neurodevelopmental delay or a behavioral response to suboptimal postnatal maternal care, we cross-fostered WT and KO pups on P1 to dams of either the same or differing genotype and assessed USVs as previously described. Although the crossfostering procedure increased the baseline frequency of vocalizations across all pup sex and age groups, KO pups reared by WT dams continued to show reduced USVs during the first postnatal week relative to WT pups reared by WT dams, while WT pups reared by KO dams produced comparable vocalization patterns to this control group. These data indicate that postnatal maternal care does not induce the observed deficit in neonate USVs, and that exposure to a postnatal *fmr1* WT maternal environment cannot rescue the reduced and delayed pattern of distress vocalization exhibited by *fmr1* KO pups. Therefore this deficit in early social communication is a potential marker of *fmr1*-dependent neurodevelopmental changes associated with adult social behavior.

Disclosures: B. Zupan: None. **A. Kashnavis:** None. **M. Morochnik:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.12/C53

Topic: A.07. Developmental Disorders

Title: Early-life inflammation affects adolescent risk seeking and alcohol consumption

Authors: *V. M. DOENNI[1], Q. J. PITTMAN[2]
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Abstract: Early-life inflammatory insults have been connected to a variety of behavioural abnormalities such as altered anxiety as well as autism- and schizophrenia-like symptoms. Previously, we were able to show that amygdala dependent behaviours (social behaviour and fear memory) are affected by exposure to endotoxin on postnatal day (P) 14. In this work we investigated whether P14 LPS alters risk assessment, another behaviour largely mediated by the amygdala. To this aim we injected animals with LPS on P14, weaned them on P21 and tested them during adolescence. In a novel object exploration task (P38-40) we found that P14 LPS increases the time animals investigate a novel item. Our preliminary data suggests that voluntary ethanol consumption may also be affected by early-life inflammation in rodents. In a two-bottle choice paradigm animals were given the option of consuming either water or water containing 10% ethanol and 1% artificial sweetener between P35 and P50. Then animals were retested for their alcohol consumption on P60. Our data indicate that the initial habituation to alcohol between P35 and P50 is not altered by P14 LPS. However, when animals were habituated during adolescence and then retested on P60, P14 LPS animals consumed significantly more alcohol than saline injected controls. We also tested whether the treatment groups or sexes will differently consume the artificially sweetened water during the same time frame. Sweetened water consumption appears to be unaffected by P14 LPS, consistent with previous findings. Risk seeking and associated addictive phenotypes are highly affected by external factors. Our data suggest that early-life inflammation may contribute to increased risk seeking and addictive behaviours in adults.

Disclosures: V.M. Doenni: None. **Q.J. Pittman:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.13/C54

Topic: A.07. Developmental Disorders

Support: DOD grant AR110189

Title: Inconsistent behavioral phenotypes in a mouse model of Fragile X Syndrome

Authors: *J. TUDOR[1,2], E. DAVIS[3,2], C. C. ANGELAKOS[2], T. A. JONGENS[4], T. ABEL[5,2]
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Abstract: A single gene knockout of the *Fmr1* gene has been used to model Fragile X syndrome. The *Fmr1* mouse model has been previously reported to have robust behavioral deficits that track Fragile X syndrome phenotypes spanning several modalities, including activity

level, motor coordination, perseveration, and cognition. Here, we measured behavior of *Fmr1* knockout mice bred on two different backgrounds. There were many behavioral phenotypes that did not replicate in our colony of *Fmr1* knockout mice. We found no significant differences in marble burying, novel object recognition, object place location memory, and behavioral flexibility in *Fmr1* knockout mice compared to wildtype littermate controls. While we observed decreased performance in the rotarod task, this phenotype was protocol-dependent. Interestingly, we found significant hypoactivity in *Fmr1* knockout mice compared to wildtype littermate controls during the dark phase. Physical phenotypes from the human disorder, such as increased weight and macroorchidism, were recapitulated in the *Fmr1* knockout mice compared to wildtype littermate controls. Together, we find that the behavioral phenotypes in the *Fmr1* knockout mice are highly variable. Thus, the continued use of this mouse model to research the underlying molecular mechanisms of behavioral deficits in Fragile X syndrome must be approached with caution.

Disclosures: J. Tudor: None. **E. Davis:** None. **C.C. Angelakos:** None. **T.A. Jongens:** None. **T. Abel:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.14/C55

Topic: A.07. Developmental Disorders

Support: NIH

Title: Postnatal critical period for social dominance plasticity in mice

Authors: *M. S. PENG[1], L. K. BICKS*[1], S. AKBARIAN[2], H. MORISHITA[3]
[1]Neurosci., [2]Psychiatry, Icahn Sch. of Med. At Mount Sinai, New York, NY; [3]Psychiatry, Neuroscience, Ophthalmology, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Many neurodevelopmental disorders such as Autism Spectrum Disorder and Schizophrenia are characterized by disruptions in social cognition. Studies in humans and animals demonstrate that the prefrontal cortex (PFC) is important in regulating social cognition, however, modeling complex social behavior development in rodents remains challenging. Here, we investigated social dominance hierarchies, known to be plastic to manipulations of synaptic efficacy in PFC, in group-housed male mice as a model of social behavior development. Using the tube test, a well-validated assay to assess dominance ranks between pairs of mice, we show that baseline hierarchies among group housed mice are more flexible during early adolescent periods and stabilize into adulthood. Social disruption specifically destabilized hierarchy during adolescence, but not in adulthood, implicating a distinct critical period of heightened plasticity in

social dominance. Using an animal model of open-ended critical period for cortical plasticity, we found heighted plasticity within adult mouse hierarchies, suggesting mechanisms regulating hierarchy plasticity are shared with other forms of cortical plasticity, such as plasticity in primary sensory areas. These results suggest that social dominance development provides a novel animal model to assess adolescent plasticity, and underlying neural correlates of social behavior maturation. *Equal first author.

Disclosures: M.S. Peng: None. **L.K. Bicks*:** None. **S. Akbarian:** None. **H. Morishita:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Topic: A.07. Developmental Disorders

Support: NIH Grant F30 MH111143

Seaver Autism Foundation

Title: Adolescent rewiring of frontal-sensory cortical projection neurons establishes adult attentional behavior

Authors: *E. NABEL[1], H. KOIKE[2], G. TACCHERI[3], Y. GARKUN[3], M. DEMARS[4], S. LOPEZ[3], H. MORISHITA[5]
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Abstract: Cortical maturation extends from adolescence into early adulthood and establishes connectivity between distal cortical areas to mediate complex cognitive processes such as attention. Notably the onset of psychiatric disorders coincides with this protracted long range development and accumulating functional and structural connectivity studies of these disorders report failed long range projection maturation. Yet limited knowledge of normal processes governing long range cortical circuit development hinders further pathophysiologic insight. Here we examine long-range cortico-cortical circuit development in a “top-down” frontal cortex projection to sensory cortex that is essential to modulate sensory processing. In the visual system, top-down neurons in the anterior cingulate cortex (ACA) directly project back to the visual cortex (VIS) to modulate visual processing, a hallmark component of visual attention. Importantly, dysregulated functional connectivity is observed between the frontal cortex and VIS during visual attention tasks in attention deficit hyperactivity disorder, schizophrenia, and autism. We thus aim to establish adolescent contributions to long-range top-down cortical circuit

maturation in murine frontal cortex and its impact on cognitive behavior later in life.
Rabies mediated circuit-specific mono-synaptic input mapping alongside dendritic spine analysis and electrophysiology interrogation reveal that top-down adolescent ACA->VIS neurons receive more local pre-synaptic connectivity coupled to higher density of post-synaptic excitatory spines on proximal dendrites compared to adulthood. These developmental changes result in a relative increase in connectivity with distal brain regions in adulthood. Transient chemogenetic inactivation of top-down cortical circuit selectively during adolescence produces long-lasting deficits in visual attentional behavior later in life at adulthood that also disrupts circuit formation. Collectively, our data demonstrate that adolescence is a key critical period for top-down cortical circuit to refine their local excitatory connectivity in an activity dependent way to engage more distal connections in order to establish adult attention behaviors. These findings may provide insight into the pathophysiology and intervention strategy for impaired visual attention in neurodevelopmental and psychiatric disorders.

Disclosures: **E. Nabel:** None. **H. Koike:** None. **G. Taccheri:** None. **Y. Garkun:** None. **M. Demars:** None. **S. Lopez:** None. **H. Morishita:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH106056

NIH Grant R01 EY024918

NIH Grant 5T32MH087004-07

Title: Parvalbumin interneurons in the prefrontal cortex control social behavior in mice

Authors: *L. BICKS[1], E. K. LUCAS[2], H. KOIKE[5], M. S. PENG[3], R. L. CLEM[6], S. AKBARIAN[4], H. MORISHITA[7]
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Abstract: Social processing is a domain that is commonly dysregulated in psychiatric disorders, and is poorly treated by available psychiatric medications. In humans and rodents, portions of the evolutionarily conserved medial prefrontal cortex (mPFC) are part of a network that regulates

social behavior. Many disorders with shared social processing deficits show impairments in inhibitory neurotransmission within the brain, particularly in the mPFC, suggesting a role for PFC inhibitory action in regulating social behavior. We investigated the role of prefrontal parvalbumin interneurons (PVIs), a major class of cortical inhibitory neurons, in social behavior of adult mice by leveraging chemogenetic technologies. First, we selectively expressed hM4Di, an inhibitory DREADD (Designer Receptor Exclusively Activated by Designer Drugs), in PVIs in the mPFC. Acute selective suppression of mPFC PVIs decreased sociability in a 3-chamber test and disrupted social recognition in a habituation-dishabituation paradigm. Suppression of PVIs did not affect olfactory discrimination, locomotion, or anxiety-related behaviors, suggesting a specific effect of PVI suppression on social behavior. We next tested whether increasing PVI activity could rescue a social deficit caused by social isolation during a 2-week adolescent window, by expressing the excitatory DREADD in mPFC-PVIs. We found activating PVIs in adult mPFC rescued a persistent social deficit induced by transient adolescent social isolation. These results demonstrate that PVI activity in the mPFC mediates appropriate social behavior in mice.

Disclosures: **L. Bicks:** None. **E.K. Lucas:** None. **H. Koike:** None. **M.S. Peng:** None. **R.L. Clem:** None. **S. Akbarian:** None. **H. Morishita:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.17/C58

Topic: A.07. Developmental Disorders

Support: NIH

Title: Frontal-sensory cortical projection neurons mediate top-down control of attentional behavior

Authors: H. KOIKE[1], K. J. NORMAN[1], S. LOPEZ[1], E. NABEL[1], M. FLANIGAN[1], Y. GARKUN[1], Z. DONG[1], M. DEMARS[1], M. G. BAXTER[1], S. J. RUSSO[1], *H. MORISHITA[2]
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Abstract: Attention is a goal-directed process that facilitates discriminatory detection of relevant sensory stimuli from the environment. Attention deficit symptoms are frequently observed in psychiatric disorders, yet finite understanding of the neural circuits mediating attentional behavior has limited pathophysiologic insight. Previous studies across species have demonstrated that the frontal cortex—especially the anterior cingulate cortex (ACC) — plays a key role in implementing attention through “top-down” control of sensory processing. However, the precise

neural circuit mechanisms effecting attention remain largely unknown. Here we identify the specific frontal cortex projecting neurons that mediate “top-down” control of visual attentional behavior in mice by integrating circuit-based techniques that monitor and manipulate neural activity in mice performing freely moving attentional behavior with a translational automated touchscreen system.
Our initial unbiased global mapping of neural activity specifically when mice are engaged in an attention task reveals recruitment of a subpopulation of ACC neurons with the long-range cortico-cortical projection to the visual cortex. Selective chemogenetic inhibition of this long range frontal-sensory cortical projection impairs attention performance, without disrupting additional detectable readouts of decision-making capacity, motivational state, motor activation, impulsivity, and compulsivity. Circuit-specific fiber photometry imaging and optogenetic rescue studies within this behavioral context are underway. Collectively, our data demonstrate that a long range frontal-sensory projection is a key enactor top-down control of attentional behavior. Our finding may provide circuit-based insight into the pathophysiology and intervention strategy for impaired visual attention in neurodevelopmental and psychiatric disorders, particularly attention deficit hyperactivity disorder, schizophrenia, and autism when dysregulated functional connectivity is observed between the frontal cortex and visual cortex during visual attention tasks.

Disclosures: **H. Koike:** None. **K.J. Norman:** None. **S. Lopez:** None. **E. Nabel:** None. **M. Flanigan:** None. **Y. Garkun:** None. **Z. Dong:** None. **M. Demars:** None. **M.G. Baxter:** None. **S.J. Russo:** None. **H. Morishita:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Program#/Poster#: 119.18/C59

Topic: A.07. Developmental Disorders

Support: P01HD057853

NSF IGERT Grant 1144399

Title: Behavioral characterization of Shank3b knockout mice

Authors: *A. R. RENDALL, P. A. PERRINO, R. H. FITCH
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by a set of core atypical social and repetitive behaviors. Individual profiles are highly heterogeneous, however, and can include language skills ranging from nonverbal to hyperlexic.

To date, causal mechanisms underlying ASD remain poorly understood, but likely include a complex combination of polygenic and environmental risk factors. Heritability rates range from 70-90%, and up to 1,000 risk genes have been identified, indicating a complex genetic architecture. One ASD-risk gene is *SHANK3* (SH3 and multiple ankyrin repeat domains 3). Heterozygous deletions or point mutations of *SHANK3* are thought to be the main cause of Phelan–McDermid Syndrome (PMS) -- a genetic disorder characterized by global developmental delays, delayed or absent speech, moderate to severe intellectual disability, dysmorphic features, neonatal hypotonia, seizures, and a strong co-morbidity with ASD. Haploinsufficiency of *SHANK3* due to deletion or *de novo* mutation is also observed in approximately 1% of non-syndromic ASD, making *SHANK3* one of the most well-replicated ASD risk genes (though *SHANK3* variants have also been linked to schizophrenia and intellectual disability). *SHANK3* is a synaptic scaffolding protein enriched in the postsynaptic density of excitatory synapses. This protein plays a crucial role in the formation, maturation, and maintenance of synapses. In order to more closely evaluate the contribution of *SHANK3* in neurodevelopment and behavior, a knockout mouse model characterized by a mutation within the PDZ domain was created by the Feng lab (Peca et al., 2011). Initial research found that genetic disruption of *Shank3* in mice leads to compulsive/repetitive behavior and impaired social interaction, thus modeling two of the core features of ASD. More recent research revealed that *Shank3B* heterozygous mice were slower to reach criterion in the pairwise visual discrimination task, and exhibited trends toward making more errors (first trial errors). These results indicate a deficit in discrimination learning in the *Shank3B* model of PMS and ASD (Copping et al., 2016). The current study was designed to further examine the behavioral profile of *Shank3B* heterozygous and homozygous knockout mice, specifically with regard to features that might map onto atypical language in ASD (auditory processing skills, learning and memory). We also examined sensorimotor ability and social behavior to confirm consistency with prior reports. We found that *Shank3B* KOs display typical auditory processing abilities, together with repetitive behaviors and learning impairments.

Disclosures: **A.R. Rendall:** None. **P.A. Perrino:** None. **R.H. Fitch:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

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Topic: A.07. Developmental Disorders

Support: NSF IGERT Grant 1144399

P01HD057853

Title: Behavioral assessment of Ush2a knockout mice

Authors: *P. A. PERRINO[1], A. R. RENDALL[1], D. NEWBURY[3], J. J. LOTURCO[2], A. BUSCARELLO[1], R. H. FITCH[1]
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Abstract: Atypical central auditory processing despite normal hearing can encompass deficits in processing rapidly changing acoustic information, as well as difficulties perceiving speech sounds in background noise. Auditory processing deficits have in turn been associated with speech and language delays, and early indices of rapid auditory processing (RAP) robustly predict later language outcomes in both typically developing and at-risk populations (Benasich et al., 2006). Auditory processing disorder (APD) is also associated with atypical speech and language outcomes, though APD may be comorbid with other disorders (e.g., attention deficits and learning disabilities). Individuals affected by APD struggle to interact in noisy group activities, impacting school performance (Moore et al., 2013). Although underlying causes for RAP deficits and ADP remain largely unknown, Newbury et al., (2015) recently reported that individuals with a heterozygous mutation of *USH2A* might show previously undetected APD, along with a distinct style of speech and severe language comprehension deficits. These results were surprising, since these individuals are carriers for Usher Syndrome but were previously thought to be phenotype-free. Usher Syndrome is an autosomal recessive form of congenital deafness and blindness that results from a mutation in *both USH2A* gene alleles, with sensory deficits emerging due to dysfunction of hair cells (stereocilia). However, since cilia also play a crucial role in neurodevelopment, and cilia dysfunction is implicated in neuronal migration anomalies relevant to neurodevelopmental disorders (e.g., dyslexia), *USH2A* carriers might show subtle and previously undetected processing deficits related to cilia dysfunction. The current study was designed to behaviorally characterize a transgenic mouse model with a heterozygous mutation of the *USH2A* mouse homolog, using a variety of tasks tapping auditory processing and learning/memory functions that could relate to APD and or RAP deficits, and might (in humans) relate to atypical language. Subjects also were assessed on social-communication and related tasks. Findings confirmed that mice with a homozygous mutation for the *Ush2a* gene were deaf, establishing the clinical validity of the mutation by confirming sensory loss in the homozygous condition. Complex behavioral findings from the heterozygous *Ush2a* mutant will be presented, with implications for future screening and intervention for carriers of Usher Syndrome.

Disclosures: P.A. Perrino: None. **A.R. Rendall:** None. **D. Newbury:** None. **J.J. LoTurco:** None. **A. Buscarello:** None. **R.H. Fitch:** None.

Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Topic: A.07. Developmental Disorders

Support: NIH Grant 1R01MH105447-01

NIH Grant T90DE022736-04

Title: Altered early life DNA methylation within the amygdala of rats predisposed to high vs. low anxiety-like behavior

Authors: *C. R. MCCOY[1], M. E. GLOVER[2], N. L. JACKSON[3], T. PTACEK[3], E. J. LEFKOWITZ[3], S. M. CLINTON[2]
[1]Sch. of Neurosci., Virginia Polytechnic Inst. and State Universit, Blacksburg, VA; [2]Sch. of Neurosci., Virginia Polytechnic Inst. and State Univ., Blacksburg, VA; [3]Univ. of Alabama at Birmigham, Birmingham, AL

Abstract: Innate differences in emotionality and temperament contribute to vulnerability to mood disorders such as depression and anxiety. Investigating heritable factors that shape temperament is essential for understanding the molecular basis of these disorders as well as novel treatment opportunities. To study neurobiological factors influencing emotionality, we use rats that were selectively-bred for high vs. low behavioral response to novelty. Low novelty responding (LR) rats exhibit high levels of behavioral inhibition and other anxiety-/depression-like phenotypes while high novelty responding (HR) rats exhibit high levels of risk-taking behavior and impulsivity. Our prior transcriptiome studies revealed marked gene expression differences in the amygdala of HR/LR rats, both during early postnatal life as well as in adulthood. We are currently investigating DNA methylation differences in the developing HR vs. LR amygdala that may drive the gene expression changes. To do so, we dissected the amygdala at postnatal days (P) 7, 14 and 21, and examined a number of DNA methylation markers in HR vs. LR rats. We first found decreased levels of DNA methyltransferase (DNMT)-3b protein and decreased global DNA methylation (5-methylcytosine) levels in the P7 HR vs. LR amygdala. Next-generation sequencing methylome profiling identified numerous differentially methylated regions across the genome in the P7 HR/LR amygdala, which confirmed a preponderance of hypomethylated regions in HR vs. LR rats. Based on these data, we hypothesized that decreased DNA methylation in the HR vs. LR amygdala contributes to their low levels of adult anxiety-like behavior. Thus, our final experiment used siRNA to transiently suppress DNMT3b mRNA in the early postnatal amygdala of normal Sprague-Dawley rats and examine its effects on adult emotional behavior. Transient early life DNMT3b knockdown enhanced adult exploratory behavior and decreased anxiety-like measures in the Open Field test and Elevated Plus Maze, but did not affect social interaction or sucrose preference. These findings highlight how inborn differences in DNA methylation may shape temperament and risk for emotional dysfunction, and may facilitate our understanding of the developmental neurobiology of emotional disorders.

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Poster

119. Neurodevelopmental Disorders: Behavioral Studies

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.21/C62

Topic: A.07. Developmental Disorders

Title: Chronic behavioral deficits, HPA axis abnormalities and altered synaptic plasticity (after 6months) in a mouse model of post-traumatic stress disorder

Authors: *M. ALGAMAL[1], J. O. OJO[1], C. LUNGMUS[1], P. MUZA[1], J. OWENS[1], B. C. MOUZON[2], D. M. DIAMOND[3], M. J. MULLAN[1], F. C. CRAWFORD[1]
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Abstract: Background: Incidence of PTSD ranges from 3-30% in groups exposed to traumatic incidents such as war, torture, or rape. PTSD is also a common neuropsychiatric disorder among military populations due to the repeated exposure to life-threatening combat-related situations. To date, there are only a few therapeutic strategies for treating PTSD, and these include the use of psychotherapy and/or pharmacotherapy. Particularly, combat-related PTSD is very refractory to these treatment approaches and although some patients might initially show some benefits, there is a high incidence of relapse in most cases. This underscore the urgent need to explore new perspectives regarding the biological responses to PTSD, and to identify new and novel therapeutic strategies. In this study, we developed a mouse model for chronic-PTSD using multiple dimensions of unpredictable stressors in the form of repeated exposures to physical, psychological and pychosocial stressors. Face and construct validity of the model were assessed at 6-month after the last stressor.
Methods: C57BL/6J male mice were exposed to a 21-day stress paradigm at 3 month of age. This involved multiple exposures to danger-related predator threat odor (TMT) whilst under restraint, daily unstable social housing with an alternate congener, physical trauma in the form of five repeated inescapable footshocks on separate days and thereafter lack of social support (single housing). Mice underwent a battery of behavioral testing for fear, anxiety and depression at 10days and 6 months post-last stressor, followed by euthanasia, and collection of brain and plasma samples for molecular profiling.
Results: Stressed mice demonstrated significant weight loss, recall of traumatic memories, anxiety and depressive-like behavior when compared to control mice. In addition, stressed mice had lower baseline plasma corticosterone and lower hipoocampal BDNF levels at 6-month after stress. Western blot analysis of hippocampus and amygdala lysates shows a dysregulation in the P75NTR/ProBDNF, TrKB/BDNF, and glutamergic signaling in stressed mice. Moreover, the GR regulatory protein FKBP51 was elevated in the amygdala of stressed mice at 6 months after stress, which supports HPA-axis dysregulation after stress.

Conclusion: Our results show that animals exposed to stressful trauma demonstrate some similar traits with the human condition as defined by DSM-V. We anticipate that our model will be a good platform to identify new targets and explore new treatment strategies in PTSD.

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Poster

119. Neurodevelopmental Disorders: Behavioral Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 119.22/C63

Topic: A.07. Developmental Disorders

Support: NIH F32-MH112232-01

NIDCD (DC009910)

Title: Unique neurobehavioral signature of maternal presence during trauma

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Abstract: Evidence across a variety of species shows that the presence of an attachment figure can buffer the effects of trauma in infants. However, repeated pairings of traumatic cues and caregiver presence, particularly in cases of caregiver abuse, can produce long-term disruptions in cognition and emotion through mechanisms that remain unclear. Using an animal model of repeated trauma with and without the mother, we observed changes in infant attachment responses to the maternal odor over time. Whereas maternal presence buffered the effects of a single presentation of shock trauma on pups' amygdala activation, USV emission, and activity levels, daily presentations of shock in the presence of the mother were associated with decreased buffering of these responses. Decreased buffering was linked with a decrease in the amygdala response to maternal odor following five days of trauma with the mother. After five days of shock with the mother, pups showed impaired attachment behaviors towards her in a social behavior test, including decreased time spent nipple-attached. These changes were accompanied by changes in amygdala structure and function, including basal c fos expression, number of immature neurons, DNA methylation, and D1 receptor levels. Furthermore, we observed increased dopamine response in the amygdala during shock trauma in pups shocked in the

presence of the mother. Central blockade of DA before trauma was able to prevent the expression of attachment behavior deficits, suggesting a therapeutic target for developing treatments and interventions for caregiver abuse.

Disclosures: M. Opendak: None. **R.E. Perry:** None. **C. Raineki:** None. **T.L. Roth:** None. **R.M. Sullivan:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.01/D1

Topic: A.07. Developmental Disorders

Support: NIH/NIAAA R01 AA09524

NIH/NIAAA R01 AA016781

NIH/NIAAA U01 AA014790

NIH/NIAAA U24 AA014815

Lycaki-Young Fund from the State of Michigan

NRF Scarce Skills Doctoral Scholarship

Title: New evidence of the role of hippocampal volume in fetal alcohol-related deficits in learning and memory

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Abstract: Disproportionate volumetric reductions in the basal ganglia, corpus callosum and hippocampus have been reported in children with prenatal alcohol exposure (PAE). However, few studies have investigated these reductions in high prevalence communities, such as the Western Cape Province of South Africa, and only one study made use of manual tracing, the gold standard of volumetric analysis. The present study examined the effects of PAE on subcortical neuroanatomy using manual tracing and the relation of volumetric reductions in these regions to performance on the California Verbal Learning Test (CVLT), a list learning task sensitive to PAE. High-resolution T1-weighted images were acquired, using a sequence

optimized for morphometric neuroanatomical analysis, on a Siemens 3T Allegra MRI scanner from 71 right-handed, 9- to 11-year-old children (9 fetal alcohol syndrome (FAS), 19 partial FAS, 24 non-syndromal heavily exposed (HE) and 19 non-exposed controls). Frequency of maternal drinking was ascertained during pregnancy using a timeline follow-back interview. PAE was examined in relation to volumes of the corpus callosum (CC) and left and right caudate nuclei, nucleus accumbens and hippocampi. All structures were manually traced using Multitracer. Higher levels of PAE were associated with bilateral reductions in caudal and hippocampal volumes, effects that remained significant after adjusting for total intracranial volume, child sex, and maternal education and smoking during pregnancy. High levels of PAE were also associated with reductions in CC volumes, but the effect on the CC was confounded by smoking during pregnancy. Performance on the CVLT was inversely related to left (r=-.34; p<.025) and right (r=-.29; p<0.05) hippocampal volumes for the exposed children but unrelated to these regional volumes for the controls. An analysis using the Sobel test showed that the effect of PAE on the CVLT was mediated by the reductions in the left (χ^2 = 1.81, p=0.07) and right (χ^2 = 2.27, p<0.025) hippocampus. These data confirm that PAE is associated with a disproportionate decrease in volume in several subcortical structures and suggest that the adverse effect of this exposure on learning and memory is partially attributable to these reductions in hippocampal volume.

Disclosures: S.C. Biffen: None. **C. Warton:** None. **N.M. Lindinger:** None. **C.D. Molteno:** None. **J.L. Jacobson:** None. **S.W. Jacobson:** None. **E.M. Meintjes:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.02/D2

Topic: A.07. Developmental Disorders

Support: NICHD/NIH Grant R01HD067731

Title: Multimodal magnetic resonance imaging in Down syndrome with full and partial trisomy 21

Authors: *L. DAI[1], ***L. DAI**[1], O. ABDULLAH[2], J. S. ANDERSON[3], M. PRIGGE[4], M. C. BURBACK[5], A. RAMIREZ[5], J. O. EDGIN[7], J. R. KORENBERG[6]
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Abstract: Down syndrome (DS) is a major cause of genetic imbalances causing brain disease throughout the lifespan: intellectual disabilities due to developmental perturbations in the young through premature aging and Alzheimer's disease (AD) in the old. Because the genetic cause of DS is known, partial or full trisomy 21, DS provides a unique opportunity to link genes to brain architectures and to cognitive and behavioral phenotypes in humans. In this report, we generate a high resolution multimodal map of brain structural Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) in a cohort of 26 subjects with full trisomy 21 (age 14-36 y/o) versus 17 age and gender matched controls, as well as five subjects with partial trisomy 21. Our results show that in addition to volumetric reduction in most regions of DS brain, we observe largely increased cortical thickness and decreased surface area which are consistent with recent report in youth DS. In addition, fractional anisotropy (FA) differ significantly in external capsule, fornix, anterior limb of internal capsule, sagittal stratum, inferior and superior cerebellar peduncle, posterior corona radiate and uncinate fasciculus. Most of decreased FA is due to increased radial diffusivity (RD), suggesting possible abnormal axon and myelination in these white matter tracts. Interestingly, the decreased FA in external capsule and uncinate fasciculus, both of which are in cholinergic pathway, are significantly contributed to deficits of memory, executive function and processing speed in DS, indicating a neural basis of the developmental deficits and possible early onset of AD in DS. Further genetic dissection using partial trisomy 21 implicate critical gene(s) associating with the brain substrates and cognitive and behavioural functions. Taken together, we hypothesize that our cognitive measures in general intelligence, memory, language will correlate with specific gene(s) and brain region patterns in DS, and therefore provide insightful information for therapeutic treatments.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: A.07. Developmental Disorders

Support: NIH Grant K01MH104592 (DJG)

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The Intellectual and Developmental Disabilities Research Center at Washington University (NIH/NICHD P30HD062171)

Tourette Association of America Research Grant (DJG)

Tourette Association of Americal Neuroimaging Consortium Pilot Grant (KJB, BLS)

Title: Patterns of functional connectivity predict maturity and diagnostic status of individuals with Tourette syndrome

Authors: *A. NIELSEN[1], J. A. CHURCH-LANG[3], N. U. F. DOSENBAH[1], K. J. BLACK[2], B. L. SCHLAGGAR[1], D. J. GREENE[2]
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Abstract: Tourette Syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics. While a common developmental course for tic symptoms has been described (i.e., onset at 6-7 years old, peak in severity at 9-11 years, improvement for many by late adolescence), TS is heterogeneous, so many patients do not follow this typical trajectory. Being able to make predictions about an individual's developmental course of symptoms would be quite useful. Previously, we demonstrated that multivariate support vector machine (SVM) learning can classify a child as having TS or not based on correlations in spontaneous fMRI activity between regions across the brain (resting-state functional connectivity: RSFC). Here, we aimed to extend this work to test if patterns of RSFC can indicate maturity and diagnostic status of individuals with and without Tourette syndrome across development. Resting state fMRI data was collected from a group of tic-free control children (C-TF; N = 39), tic-free control adults (A-TF; N = 39), children with Tourette syndrome (C-TS; N = 39), and adults with Tourette syndrome (A-TS; N = 39). RSFC data among 264 previously defined regions underwent volume censoring and strict preprocessing to minimize motion-related artifact. While SVM is most commonly used to predict binary class labels, it can be extended to predict multiple classes (mc-SVM). We used mc-SVM to create a multivariate model separating C-TF, C-TS, A-TF, and A-TS individuals with RSFC and tested this model with leave-one-out cross validation. The mc-SVM model was able to classify individuals according to maturity and diagnostic status with 64% accuracy (chance=25%). Classification accuracies for the 4 groups are shown in Figure 1. Individuals were more likely to be misclassified according to diagnostic group than age group. The way in which an individual is misclassified with mc-SVM provides a richer characterization of the individual than binary SVM, which may be useful for predicting the clinical outcomes and developmental course of symptoms for TS individuals.

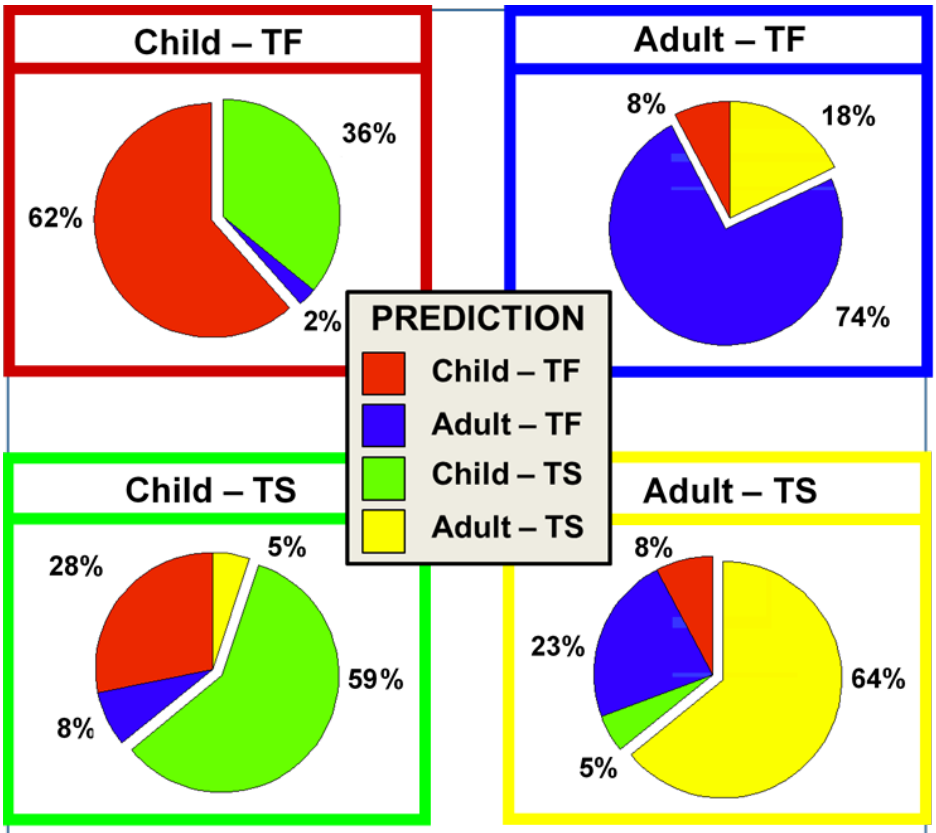

Figure 1. *Prediction of maturity and diagnostic status in C-TF, A-TF, C-TS, and A-TS individuals. E*ach quadrant depicts how individuals within a given class were classified according to their RSFC with mc-SVM.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.04/D4

Topic: A.07. Developmental Disorders

Title: Neural correlates of abstract social cognition in Williams syndrome and 7q11.23 Duplication syndrome

Authors: *D. CURRIN[1], T. NASH[1], M. JABBI[1], D. P. EISENBERG[1], M. GREGORY[1], K. V. ROE[1], R. PRABHAKARAN[1], J. CARRASCO[1], O. RAVINDRANATH[1], S. GROGANS[1], M. O'BRIEN[1], J. S. KIPPENHAN[1], P. KOHN[1], A. MARTIN[1], C. MERVIS[2], K. F. BERMAN[1]

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Abstract: Hemideletion (yielding one copy of affected genes) or duplication (three gene copies) of ~25 genes at chromosomal location 7q11.23 causes Williams syndrome (WS) or the 7q11.23 Duplication syndrome (DUP7), respectively. While children with WS show hypersociability and increased empathy, children with DUP7 have reduced sociability and a tendency toward systemizing, similar to children with autism spectrum disorders. To elucidate the neural substrate of these hallmark social-cognitive features, we used fMRI to study abstract social cognition in children with WS and DUP7, as well as typically developing (TD) children. We also tested for group differences in systemizing scores, and explored whether these scores related to neural response.

During 3T fMRI, 13 children with WS (age=13.5±3.6, 10 girls), 31 TD children (age=13.9±3.6, 13 girls), and 11 children with DUP7 (age=12.9±3.1, 5 girls) watched videos of moving geometric shapes that could be interpreted as social interactions, and, as a control task, videos of the same shapes moving randomly. Participants completed a post-scan questionnaire documenting the extent to which they perceived the geometrical shapes as social constructs. We also derived a systemizing score (SQ) for each participant using the Empathizing Quotient-Systemizing Quotient Questionnaire (EQ-SQ). After preprocessing with SPM5, we ran ANOVAs to test for group differences in BOLD activation (social vs. control tasks, $p < 0.001$ uncorrected). In addition, we tested for relations between social agency count (SAC), EQ-SQ scores, and BOLD signal. All data were controlled for age and sex.

There were group differences in the middle temporal gyrus (MTG) bilaterally, and post-hoc t-tests revealed a step-wise difference related to gene dosage in the right MTG with DUP7<TD ($p = 0.04$) and TD<WS ($p = 0.007$). SQ scores differed across groups ($p < 0.001$) with DUP7 having the highest scores (DUP7 mean = 30.9±4.7, TD = 25.0±9.0, WS = 13.4±6.6). In DUP7, as SQ score increased, BOLD activation in the right MTG also increased ($r = 0.834$, $p = 0.005$), while the converse relationship was found in the TD group ($r = -0.388$, $p = 0.046$), and there was a between-group difference in these relationships ($p < 0.001$). Further, as SQ scores increased in the TD group, SAC decreased ($r = -0.51$, $p = 0.008$). This relationship was also found in the WS group ($r = -0.646$, $p = 0.044$).

These findings of differential neural activation during the processing of abstract social scenes in WS and DUP7 may provide clues about the neural underpinnings of the syndromes' contrasting socio-emotional phenotypes. Future work will assess longitudinal trajectories of this socio-emotional circuitry.

Disclosures: **D. Currin:** None. **T. Nash:** None. **M. Jabbi:** None. **D.P. Eisenberg:** None. **M. Gregory:** None. **K.V. Roe:** None. **R. Prabhakaran:** None. **J. Carrasco:** None. **O. Ravindranath:** None. **S. Grogans:** None. **M. O'Brien:** None. **J.S. Kippenhan:** None. **P. Kohn:** None. **A. Martin:** None. **C. Mervis:** None. **K.F. Berman:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.05/D5

Topic: A.07. Developmental Disorders

Support: NIMH Intramural Research Program

Title: Copy-number variation in the Williams syndrome critical chromosomal region 7q11.23 impacts resting-state functional connectivity and associated structural connectivity measured with DTI tractography

Authors: *J. S. KIPPENHAN[1], M. GREGORY[1], T. NASH[1], R. PRABHAKARAN[1], C. MERVIS[2], D. EISENBERG[1], O. RAVINDRANATH[1], D. CURRIN[1], S. GROGANS[1], M. O'BRIEN[1], P. KOHN[1], K. F. BERMAN[1]
[1]IRP/NIMH/CTNB/Section on Integrative Neuroimaging, NIH, Bethesda, MD;
[2]Neurodevelopmental Sci. Laboratory, Dept. of Psychological and Brain Sci., Univ. of Louisville, Louisville, KY

Abstract: In Williams syndrome (WS), a 1.5 megabase *hemideletion* at chromosomal location 7q11.23 leaves individuals with one copy of ~25 genes located in this region, while in 7q11.23 duplication syndrome (Dup7), *duplication* of the same chromosomal region imparts three copies. These contrasting copy number variations (CNVs) are accompanied by contrasting phenotypes: WS is characterized by hypersociability and severe visuospatial construction deficits, whereas Dup7 has been associated with social phobia and relatively preserved spatial abilities (Mervis 2015), and has been shown to be a risk factor for autism spectrum disorders (Sanders 2011). Previous WS studies have shown structural and functional deficits in the intraparietal sulcus (IPS) that are associated with visuospatial deficits (Meyer-Lindenberg 2004, Kippenhan 2005), and structural and functional variations in the insula that appear to impact social/emotional processing (Jabbi and Kippenhan 2012). We acquired resting-state fMRI (rsFMRI) and diffusion (DTI) MRI scans from 19 children with WS (mean age=11.7±3.4, 12 girls), 12 children with Dup7 (age=13.2±3.1, 5 girls), and 19 typically developing (TD) children (age=12.3±3.2, 10 girls). We performed connectome-wide association analysis (CWAS) (Shehzad 2014) on the rsFMRI data (covarying for age and sex) to identify brain regions where functional connectivity (FC) was significantly associated with 7q11.23 gene dosage, performed DTI tractography based on these regions, and did ANCOVA analyses on fractional anisotropy (FA) along the computed tracts, covarying for age and sex. The rsFMRI-based CWAS analysis revealed 11 regions in which FC was significantly associated with 7q11.23 CNV ($p<0.05$ Bonferroni corrected): bilateral IPS, visual area V4, insula, and supramarginal gyrus, as well as posterior cingulate cortex, right superior frontal gyrus, and left anterior cingulate cortex. ANCOVA showed a

significant effect of CNV (p=0.00008) on FA values within the network of gray-matter CWAS-based ROIs. Post-hoc analysis revealed the largest FA-based differences were between (1) left insula and left supramarginal gyrus (WS > TD, p=0.02 and WS > Dup7, p=0.04), and (2) right IPS and right V4 (WS < TD, p=0.0008 and WS < Dup7, p=0.03). These variations in structural and functional connectivity, associated with 7q11.23 CNV in both visuospatial (IPS, V4 regions) and social/emotional (insula region) networks, provide evidence for specific impacts of 7q11.23 gene dosage on networks relevant to the visuospatial and social/emotional phenotypes found in WS and Dup7. Future work will include longitudinal assessment of these CNV-related variations.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.06/D6

Topic: A.07. Developmental Disorders

Support: National Institutes of Health (NIH) Consortium grant U54 EB020403

European College for Neuropsychopharmacology (ECNP) by a grant for the ECNP Network ADHD Across the Lifespan

Title: Brain alterations in ADHD and their link to genetics

Authors: *M. HOOGMAN[1], M. KLEIN[2], J. BRALTEN[2], E. SHUMSKAYA[2], J. L. STEIN[3], R. K. WALTERS[4], H. ADAMS[5], T. ENIGMA-ADHD WORKING GROUP[2], T. ENIGMA CONSORTIUM[6], T. CHARGE CONSORTIUM[7], T. ADHD WORKING GROUP PGC[8], T. IPSYCH CONSORTIUM[9], A. BORGLUM[9], S. MEDLAND[10], J. K. BUITELAAR[11], A. ARIAS-VASQUEZ[12], S. V. FARAONE[13], P. SHAW[14], P. THOMPSON[15], B. FRANKE[2]
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Aarhus, Denmark; [10]Quantitative Genet. Laboratory, QIMR Berghofer Med. Res. Inst., Bisbane, Australia; [11]Radboud university medical center, Donders Inst. for Brain, Cognition and Behaviour, Dept. of Cognitive Neurosciences, Nijmegen, Netherlands; [12]Radboud university medical center, Donders Inst. for Brain, Cognition and Behaviour, Dept. of Psychiatry, Nijmegen, Netherlands; [13]Departments of Psychiatry and of Neurosci. and Physiology, SUNY Upstate Med. University, Syracuse,, Syracuse, NY; [14]Natl. Inst. of Mental Health, Bethesda, MD,USA, Bethesda, MD; [15]Imaging Genet. Center, Dept. of Neurology, Keck Sch. of Medicine, Univ. of Southern California, Marina del Rey, CA, USA, Marina de Rey, CA

Abstract: Introduction Neuroimaging studies show structural alterations of various brain regions in children and adults with ADHD. However, these studies are often underpowered and their methods heterogeneous. After examining subcortical structures, the ENIGMA-ADHD Working Group now also presents a study of cortical measures across the lifespan in a large, cross-sectional ADHD sample. To explore the etiology of those brain differences, we investigated the overlap between common genetic variation associated with ADHD risk and brain volume measures.
Methods A total of 35 sites from around the world have joined our Working Group, and used fully automated and validated segmentation software (FreeSurfer) to segment the brain. Subcortical (volume) and cortical brain measurements (thickness and surface area) were compared between cases (n=1932) and controls (n=1932), and also separately for children (<11 years), adolescents (12-17 years) and adults (≥18 years). To investigate the overlap between common genetic variation associated with ADHD risk (N=55,374; PGC+iPSYCH ADHD working groups) and brain volume measures (N=11,221-24,704; ENIGMA and CHARGE consortium), we used a set of complementary methods, extending a recent analysis of schizophrenia.
Results We found subtle but significantly reduced thickness values in the temporal pole, fusiform gyrus, pre-and paracentral gyrus and entorhinal cortex (effect size ranging from Cohen's *d* -0.09 to -0.15) and overall reduced surface area (Cohen's *d*: -0.21). Differences were most pronounced in children (maximum effect size: -0.30 for surface area). Linkage disequilibrium score regression revealed a negative genetic correlation between ADHD and intracranial volume (ICV) (-0.206; $P=2x10^{-10}$). SNP effect concordance analysis showed significant pleiotropy and concordance of allelic effects between ADHD risk variants and variants associated with smaller ICV (both P=0.0009). Significant concordant genetic effects were also seen for nucleus accumbens volume (P=0.0009). Gene-set analysis, using ADHD-ICV meta-analytic summary statistics, showed significant association of the neurite outgrowth gene-set ($N_{genes}=44$; P=0.0025).
Conclusions In the largest study of brain imaging in ADHD, we report differences in several temporal and frontal regions between ADHD patients and controls. All differences had small effects sizes, and were largest in children. Our results show significant genetic covariation between ADHD and ICV, possibly linked to neurite outgrowth signaling. Our findings can help us to develop new hypotheses about biological mechanisms underlying ADHD.

Disclosures: M. Hoogman: None. **M. Klein:** None. **J. Bralten:** None. **E. Shumskaya:** None. **J.L. Stein:** None. **R.K. Walters:** None. **H. Adams:** None. **T. ENIGMA-ADHD working**

group: None. **T. ENIGMA Consortium:** None. **T. Charge consortium:** None. **T. ADHD Working Group PGC:** None. **T. iPSYCH consortium:** None. **A. Borglum:** None. **S. Medland:** None. **J.K. Buitelaar:** None. **A. Arias-Vasquez:** None. **S.V. Faraone:** None. **P. Shaw:** None. **P. Thompson:** None. **B. Franke:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.07/D7

Topic: A.07. Developmental Disorders

Title: Prediction of therapeutic efficacy of methylphenidate in ADHD patients using electroencephalogram

Authors: Y. TAKAHARA[1], T. OTA[2], Y. NAKANISHI[2], S. UEDA[2], P. JURICA[3], Z. R. STRUZIK[3], K. NISHITOMI[1], J. IIDA[2], T. KISHIMOTO[2], A. CICHOCKI[3], M. HASEGAWA[1], *K. OGAWA[1]
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Abstract: Psychiatric disorders, including Attention-Deficit / Hyperactivity Disorder (ADHD), were diagnosed according to standard diagnostic criteria like Diagnostic and Statistical Manual of Mental Disorders (DSM-V) based on “visible symptom”. Patients represented the similar “visible symptom” were categorized into same diagnosis, and consequently wide variety of patients with different symptom and biological background was exist in the same disease. This heterogeneity of patients results in the limited therapeutic efficacy of medication in psychiatric disorders, and it is important to classify the heterogeneous patients based on biological background. Electroencephalogram (EEG) is noninvasive tools to evaluate human brain activities and functions, and has a potential to characterize the heterogeneous patients in psychiatric disorders based on brain activity. Previously, a large number of reports show EEG abnormalities in ADHD, and recently FDA approved theta/beta ratio as the EEG marker for assistance of ADHD diagnosis. However, the EEG markers related to therapeutic efficacy was not fully clarified. Here we carried out EEG recordings of ADHD patients in combination with the evaluation of their ADHD rating scales (ADHD-RS) before and after medications. Firstly, we compared EEG patterns of typical development subjects (healthy children) with these of ADHD patients and identified several EEG indices with significant differences, including theta/beta ratio. Next, we studied the differences of EEG patterns and ADHD-RS between before and after methylphenidate (MPH) treatments. After 8±2 weeks treatment of MPH, ADHD-RS were significantly improved, however there was no significant change on any EEG indices. Then, we divided ADHD patients into MPH positive patients and MPH negative patients according to the

therapeutic efficacy on ADHD-RS and clarified quite different EEG patterns in alpha band and delta coherence before the MPH treatment started. In this study, we demonstrated that heterogeneity of ADHD patients in terms of therapeutic efficacy of MPH and corresponding EEG patterns at pretreatment phase. The result was from pilot study with small number of patients, but has great potential of EEG to characterize heterogeneous psychiatric disorder patients more appropriately and lead to more precise medication based on biological background.

Disclosures: **Y. Takahara:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD.. **T. Ota:** None. **Y. Nakanishi:** None. **S. ueda:** None. **P. Jurica:** None. **Z.R. Struzik:** None. **K. Nishitomi:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD.. **J. Iida:** None. **T. Kishimoto:** None. **A. Cichocki:** None. **M. Hasegawa:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD. **K. Ogawa:** A. Employment/Salary (full or part-time):; SHIONOGI & CO., LTD..

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.08/D8

Topic: A.07. Developmental Disorders

Title: Impaired attention-related connectivity in children with ADHD: An fNIRS study for potential diagnostic predictor

Authors: S. SUTOKO[1], T. FUNANE[1,2], T. KATURA[1], *H. SATO[1], M. KIGUCHI[1], A. MAKI[1], Y. MONDEN[2], M. NAGASHIMA[2], M. UGA[4,5], T. TOKUDA[4], T. YAMAGATA[2], I. DAN[4,3]
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Abstract: In pediatrics, attention deficit/hyperactivity disorder (ADHD) is one of major concerns due to its high prevalence rate and complexity of diagnosis in co-morbidity. Disorder management which emphasizes the urgency of early diagnosis comprehensively attempts the improvement and maintenance of quality of life (QoL). By aiming the development of personal ADHD diagnostic tool, we used a functional near-infrared spectroscopy (fNIRS), a non-invasive functional imaging technique with less noisy measurement practice especially for neonates and disordered children, to investigate the relationship between brain activation - connectivity and ADHD identification. The measurement was done with two-plane probe covering both frontal-to-parietal lobes to monitor brain activity - connectivity of 37 children with ADHD (9.68 ± 2.01 years old) and 22 typical developing (TD) children (9.91 ± 1.87 years old) while performing the oddball task, an attention measure. We confirmed the significant activation on right

inferior/middle frontal gyri (IFG/MFG) and right supramarginal/angular gyri (SMG/AG) during the task in TD children, whereas children with ADHD had decreased activation on corresponding regions. The common functional connectivity analysis solely focuses on the high correlation representing the strong linearity between two brain regions. However, we found that two regions might likely be connected and yet those could be either activated or inactivated together as happened in TD and ADHD children, respectively. Therefore, the current analysis selectively highlighted the connectivity strength as the attention-related activation occurred and oppositely suppressed the quantified connectivity if the mutual inactivation was recognized. TD children showed superior attention-related connectivity in inter- and intra-hemisphere involving right and left IFG/MFG and right SMG/AG (i.e., attention nodes) compared to ADHD children. The connectivity strength of related attention nodes was computerized as a diagnostic index and we found the promising accuracy performance - correct classification between ADHD and TD children in both training (79.1%; 15 samples) and validation (76.7%; 22 samples) datasets. Our findings suggested that the highly synchronized regions may not always associate with the dependent-activation and the well-performed ADHD diagnostic predictor relies on both features of brain activation and functional connectivity in bilateral frontal and right posterior parietal cortices.

Disclosures: S. Sutoko: None. **T. Funane:** None. **T. Katura:** None. **H. Sato:** None. **M. Kiguchi:** None. **A. Maki:** None. **Y. Monden:** None. **M. Nagashima:** None. **M. Uga:** None. **T. Tokuda:** None. **T. Yamagata:** None. **I. Dan:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

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Program#/Poster#: 120.09/D9

Topic: A.07. Developmental Disorders

Title: Impact of comorbid autism spectrum disorder on event-related potentials in attention-deficit/hyperactivity disorder

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Abstract: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are two of the most commonly diagnosed childhood neurodevelopmental disorders. In the last decade, research has revealed that the prevalence of ADHD and ASD has increased, and an increasing number of cases of comorbid ADHD and ASD has been reported. Although the

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) precluded co-morbid diagnosis of ADHD and ASD (ADHD/ASD), the fifth edition of the DSM (DSM-5) allows clinicians to diagnose ADHD and ASD simultaneously. Despite this important change, still relatively little is known about the neurobiological basis of overlap between these conditions. The Autism Treatment Network database suggests that individuals who have ADHD/ASD tend to have poorer adaptive functioning and lower quality of life compared with those who have ASD alone. Thus, we hypothesized that a comorbid ASD had a negative effect on event-related potentials (ERP) in ADHD which correlate with severity of ADHD symptoms, particularly impulsivity. We evaluated auditory oddball task performance via ERP in 31 and 17 patients with ADHD and ADHD/ASD, respectively, and 22 healthy controls matched for age and sex. We measured P300 and mismatch negativity (MMN) amplitude during the task. Clinical psychopathology was evaluated using the ADHD Rating Scale-IV-Japanese version and Child Autism Rating Scale. The ADHD/ASD group showed greater P300 amplitude attenuation at Cz and poorer P300 task performance relative to that of the ADHD group. Both patient groups showed greater P300 and MMN amplitude attenuation and longer latency in several positions relative to that of the control group. Moreover, ERP measurements were positively correlated with ADHD hyperactivity-impulsivity subscale scores. Our findings suggested that ERP measurement could be used to differentiate between patients with ADHD/ASD and ADHD, providing new insight into impulsivity in ADHD and/or ASD.

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Poster

120. Neurodevelopmental Disorders: Human Studies

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Program#/Poster#: 120.10/D10

Topic: A.07. Developmental Disorders

Support: NSFC Grant 81302437

NSFC Grant 81673197

Title: The white matter connectivity in Chinese children with developmental dyslexia

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Abstract: *Background* The deficits of brain structure in children with developmental dyslexia (DD children) still remain unknown.Updated magnetic resonance imaging (MRI) techniques

have provided multiple new possibilities to study reading-relevant neural networks in DD children by analyzing white matter changes using diffusion tensor imaging (DTI). However, as a logographic writing system, Chinese character is different from western alphabetic writing system. It is unclear whether Chinese DD children have different effects on the white matter structure of human brain. *Methods* 15 DD children and 11 typically developing children were enrolled the study. Diffusion tensor imaging (DTI) was used to measure the white matter structure of the brain in Chinese dyslexic children. Fractional anisotropy (FA) was used to analyze the DTI data. *Results* Compared to typically developing children, DD children had lower FA in bilateral inferior fronto-occipital fasciculus (IFOF) , bilateral cingulum, the left superior longitudinal fasciculus and the right inferior longitudinal fasciculus. *Conclusion* Chinese DD children exist linking atypical white matter microstructure in bilateral temporo-parietal white matter structure. Chinese DD children have different deficits of the brain construction from DD children using alphabetic writing.

Disclosures: **X. Hu:** None. **J. Chu:** None. **J. Wu:** None. **X. Zhao:** None. **M. Fan:** None. **X. Li:** None.

Poster

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Topic: A.07. Developmental Disorders

Support: 973 program (2014CB846103)

Title: Alterations in the large-scale brain functional network in Chinese dyslexic children in reading tasks

Authors: *H. JIALI, X. LIU, Y. GAO, Q. DI, L. LIU
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Abstract: Dyslexia is a specific reading difficulty, which showed parallel deficits in both orthography-to-phonology and orthography-to-semantics mapping. Previous functional connectivity studies suggest that dyslexia is a disconnectivity syndrome. However, traditional connectivity studies tended to focus on the selected seed regions instead of concerning interaction of whole brain regions by using graph theoretical analysis. In our study, we adopted a semantic relatedness rhyming judgment and a semantic relatedness judgment task to examine the Chinese dyslexic alteration of functional brain network during reading from a large-scale perspective. Sixteen typically developing children and fifteen dyslexic children were included. Participants were asked to perform reading tasks in fMRI scanners while their brain were imaged. The findings are as follows: First, typically developing children’s brain connectivity was

more similar to that of dyslexic children in semantic relatedness judgment task than in rhyming. Specifically, the two groups only shared 33 percentages of common hubs in rhyming task but shared 76 percentages of common hubs in semantic task, which indicates that Chinese dyslexia have larger alteration in phonological than in semantic processing. Of note, hubs were essential nodes in a brain.Second, only typically developing children showed between-task differences in inter-regional connectivity, whereas dyslexic children did not show any task difference, suggesting the topological organization of typically developing children's reading network is more specialized than that of dyslexia. Last, through comparing participants' performance between rhyming and semantic task, different brain network patterns were used in two groups. Typically developing children respectively showed stronger long-distance and stronger short-distance interregional connectivity during rhyming and semantic task. When it comes to dyslexic children, their brain network pattern did not show distinctly difference during different reading tasks. Supplementary motor area, rectus, hippocampus, precentral and frontal areas played important roles in both tasks.Some of the aforementioned brain network alterations of dyslexic children have been reported in previous studies using task-free resting state data, suggesting it may be domain-general. Taken together, our study suggests that Chinese reading dyslexia showed great alteration in brain connectivity properties, and some of these alterations may be domain-general while others may be modulated by different reading tasks.

Disclosures: **H. Jiali:** None. **X. Liu:** None. **Y. Gao:** None. **Q. Di:** None. **L. Liu:** None.

Poster

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CNPq 455687/2014-5

Title: Dual task on postural sway and eye movement in dyslexic children

Authors: *J. A. BARELA[1,2], M. RAZUK[1,3], H. PEYRE[4], C. L. GERARD[4], M. P. BUCCI[3]
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Abstract: The aim of the study was to verify the effects of three different visual tasks on body sway in dyslexic children. Fifteen dyslexic and 15 non-dyslexic children were asked to stand upright or sitting (baseline) condition in front of an LCD monitor, 60 cm away and at eye level. All children performed three experimental visual conditions: reading task (silent reading of a text project on the monitor); *Landolt* reading-like task (all letters of the reading task being replaced by close circles and some Landolt´s rings) and children were asked to scan each stimulus in a reading-like fashion from the left to the right and count the amount of Landolt's rings; and fixation task (gaze in a white circumference of 1.5 cm). The experimental conditions were repeated two times, lasting 30 seconds each. Eye movements were recorded binocularly by Mobile EyeBrain Tracker (Mobile T2®, SuriCog). The excursions of the center of pressure (CoP) were recorded with Multitest Equilibre (Framiral®, Grasse, France). Postural recording was performed on both stable and unstable platform. The dependent variables for visual performance in reading of a text and *Landolt* reading-like were: reading time, duration of fixation, number of pro- and retrosaccades, amplitudes of prosaccades; while for fixation condition was number of saccades. The dependent variables for postural performance were: area and mean speed of the CoP. The results showed that dyslexic children read slower in both visual condition tasks (reading and *Landolt*-reading like) than non-dyslexic children. Dyslexic children made shorter fixation than non-dyslexic children, especially in sitting condition than in other posture condition. Furthermore, dyslexic children made more pro-saccades than non-dyslexic children and dyslexic children made more retro-saccades in unstable condition than in stable condition. Dyslexic children made less amplitude of pro-saccades than non-dyslexic children. Finally, dyslexic children showed smaller CoP area in the reading silent visual condition in unstable condition and higher velocity than non-dyslexic children. These results indicate that dyslexic children are able to modulate body sway in performing reading task, suggesting that the stimulus projected on the monitor was used as additional sensory cues to improve postural control system functioning specially in a more difficult posture condition (upright unstable). We can suggest that dyslexic children put more resources attentional in posture than in cognitive task in unstable condition, and consequently, improved posture and decrease cognitive task (higher number of retro-saccades).

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Poster

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Program#/Poster#: 120.13/D13

Topic: A.07. Developmental Disorders

Support: Alexander von Humboldt Foundation

Alan & Wendy Pesky

Title: Impact of orthography and dyslexia on virtual maze performance

Authors: *L. A. GABEL[1,2], C. GOERNER[3], A. BATTISON[4], S. HORNDASCH[2]
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Abstract: Recent research findings indicate a higher incidence rate of phonological dyslexia in English, a non-transparent language, as opposed to surface dyslexia typically identified in children from countries with transparent languages (e.g. Finnish, Spanish, German). Transparency is defined by the consistency of phoneme-grapheme correspondence in a given language. Dyslexia is associated a difficulty understanding the sound structures of words, which may impair the ability to segment (breaking up words in smaller segments) and blend (bringing segments together) words. Children with dyslexia exhibit impaired working memory ability. Altered learning and memory may influence the ability to segment and blend smaller segments of words, resulted in impaired reading ability. Our recent data suggest that animal models of the disorder (i.e. mice with a mutation within the DCDC2 gene) are impaired at a Hebb-Williams (HW) maze, a visuo-spatial learning and memory task. These results were translated to the human population using a virtual version of this task (vHW). English-speaking children (5-13 years of age) with reading impairment display altered visuo-spatial learning and memory performance on the vHW maze task. In the present study we examined both vHW maze performance, and genetic risk variants in native-German speaking children (5-13 years of age). Participants in this study attended either public school (German speaking), or an international school (English speaking) in Bavaria, Germany. Our data suggest that impairment on the vHW maze task may be consistent across language orthographies. Native-German speaking children exhibit similar performance efficiencies on the vHW maze task when compared to native-English speaking children. Children with reading impairment, regardless of their language background, displayed impaired performance on this task. These data suggest a general impairment across language orthographies (transparent and non-transparent orthography), and provide valuable information toward the understanding of dyslexia.

Disclosures: L.A. Gabel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Provisional Patent 62/475,553. **C. Goerner:** None. **A. Battison:** None. **S. Horndasch:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

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Topic: A.07. Developmental Disorders

Support: M.FE.A.NEPF0001

Title: Detecting cortical facets of developmental disorders using multivariate random forest classification: The case of dyslexia

Authors: *U. KUHL, ***U. KUHL**, A. D. FRIEDERICI, M. A. SKEIDE
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Abstract: Cortical thickness has been the core variable of interest for finding structural signatures of dyslexia (Altarelli et al., 2013, Clark et al., 2014; Kraft et al., 2015). The role of other morphological measures, however, remains elusive. While there is some evidence for abnormal gyrification in dyslexic children (Im et al., 2015; Williams et al., 2017), little is known about possible contributions of sulcus depth or surface folding complexity, measures associated with other major developmental disorders such as autism (Ludwig et al., 2013; Nordahl et al., 2007). Here we recorded T1-weighted structural MR images from 16 dyslexic children (5 female) and 16 controls (7 female). To disentangle potential causes from consequences of dyslexia, these data were analyzed at two time points, namely at a preliterate age (5.0-6.4y) and at the end of second grade (7.11-9.1y). We estimated four surface-based grey matter features: cortical thickness, cortical complexity, gyrification index and sulcus depth (Dahnke et al., 2012; Luders et al., 2006; Yotter et al., 2011). Employing a multivariate method to determine areas with distinct patterns of cortical surface anatomy, these features were then used to train vertex-wise random-forest classifiers (Breiman, 2001). This innovative approach allows determining the individual contribution of each feature to final classification accuracy in a single model. Our results reveal a co-occurrence of transient effects only present at a preliterate age and stable effects persisting into second grade. While transient differences (maximum accuracy: 85%) were observed in the left occipito-temporal cortex close to the “visual word form area” (Skeide et al., 2016), persisting differences were observed in phonological processing areas (superior temporal sulcus; maximum accuracy: 82.5%) (van Attefeldt et al., 2004) and semantic processing areas (angular gyrus; maximum accuracy: 90%) (Carreiras et al., 2009). Crucially, we provide first evidence that successful classification is often driven by a combination of different features rather than individual features alone. In sum, we provide a powerful unified framework for simple early detection of cortical features characterizing developmental disorders.

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Poster

120. Neurodevelopmental Disorders: Human Studies

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Topic: A.07. Developmental Disorders

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Title: Synergistic adverse fetal neurodevelopmental effects of maternal depression and obesity

Authors: *N. MERABOVA[1], G. TATEVOSIAN[1], N. DARBINIAN[1], L. GOETZL[1,2]
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Abstract: **Introduction**: Maternal obesity (MO) and depression (MD) have independently been associated with pediatric neurodevelopmental sequelae. Both are growing public health concerns with overlapping psychosocial and pathophysiologic etiologies. Complex biological mechanisms including adipokines may mediate the association between obesity and depression with neurodevelopmental implications. Our previous data on Adiponectin (AdipoQ) in pregnancy led us to hypothesize that *in utero* exposure to MO and/or MD would alter neural expression of genes involved in AdipoQ signaling pathway and autophagy dysregulation.
Methods: We performed an IRB-approved, matched case-control study in women undergoing elective pregnancy termination in the second trimester (gestational age (GA) 15 - 21 weeks). Serum and snap-frozen fetal brain tissue were collected in women with self-reported MD. Samples were further characterized by maternal body mass index (BMI ≤ 24.9/lean vs ≥30/obese). Controls (CNTRLs) were matched for GA & BMI to form 4 groups: lean MD (2♂/1♀), obese MD (3♂/2♀), lean CNTRLs (2♂/1♀), and obese CNTRLs (3♂/2♀). Maternal serum AdipoQ was quantified by ELISA. Total RNA was isolated from snap-frozen fetal brain tissue. RT-PCR was performed with specific primers.
Results: Mean serum AdipoQ was highest in lean CNTRLs (11.6±1.0 μg/mL). AdipoQ was lower in either obese CNTRLs (5.7±0.9 μg/mL) or lean MD (7.0±0.9μg/mL), but the combination of exposures (MO/MD) resulted in a synergistic suppression (2.7±0.2 μg/mL, $p<0.001$ overall, post hoc comparisons all $p<0.005$). Fetal brain gene expression showed the following patterns (**Table1**): *ADIPOR1* and *ADIPOR2* were both up regulated by MD without a clear pattern related to MO. In contrast, autophagy related genes *BECN1* and *ATG7* were both significantly down regulated by MD and there appears to be a synergistic effect with MO.
Conclusions: *In utero* exposure to the combined hits of MO and MD is associated with suppressed maternal AdipoQ and potentially clinically significant alterations in fetal brain expression of genes in the adiponectin and autophagy signaling networks. These molecular

alterations may provide a better understanding of the interrelation between MO and MD and neurodevelopmental and behavioral outcomes.

Table 1. Gene Expression in Utero Exposure to MD

Gene	Lean			Obese		
	Fold	p-value	SEM	Fold	p-value	SEM
ADIPOR1	1.6	0.01	0.19	2.6	0.02	0.73
ADIPOR2	2.4	0.02	0.31	1.7	0.05	0.63
BECN1	-1.5	0.05	0.15	-4.9	0.05	0.07
ATG5	-4.8	0.1	0.06	-4.3	0.12	0.12
ATG7	-2.3	0.0004	0.01	-3.2	0.03	0.09

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Poster

120. Neurodevelopmental Disorders: Human Studies

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Topic: A.07. Developmental Disorders

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Title: Sex specific effects of maternal cortisol concentrations during pregnancy on the functional connectivity of the newborn limbic system

Authors: *A. GRAHAM[1], J. RASMUSSEN[2], S. ENTRINGER[3], M. G. RUDOLPH, 97215[4], M. STYNER[5], J. H. GILMORE[6], S. G. POTKIN[7], P. WADHWA[8], D. A. FAIR[9], C. BUSS[10]

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Abstract: Background. Identifying prenatal influences on the rapidly developing fetal brain is important for understanding the etiology of psychiatric disorders. Maternal cortisol levels during pregnancy are of particular interest for understanding developmental origins of sex differences in psychiatric disorders as maternal-fetal cortisol signaling appears to differ depending on fetal sex. We examined sex-specific associations between maternal cortisol concentrations throughout pregnancy and coordinated functioning of the limbic system in newborn infants. **Methods.** Data were from an ongoing longitudinal study of maternal-fetal/infant-dyads (N=70 infants;32 females). Average maternal cortisol output during pregnancy was estimated as mean area under the curve (AUC) derived from 5-daily saliva samples on 4-days in each trimester. Resting state functional connectivity MRI was examined in neonates (gestational age at birth=39.2+/-1.5, scan age=3.79+/-1.84 weeks) using individually segmented amygdala and hippocampus seeds. **Results.** Significant interactions between maternal cortisol and infant sex were identified for the functional connectivity of the amygdala and hippocampus ($p<0.05$ with monte carlo simulation for multiple comparisons corection). For females, higher maternal cortisol was associated with increased amygdala and hippocampal functional connectivity to brain regions within the default mode network (DMN), most consistently for posterior cingulate cortex. For males, higher maternal cortisol concentrations were associated with weaker amygdala and hippocampal connectivity to DMN regions. **Conclusions.** The distinct pattern of integrating versus segregating limbic regions from a large scale cortical brain system may reflect unique strategies for males versus females in adapting to a stressful environment signaled by heightened maternal cortisol during pregnancy. Building on these findings, we are currently examining associations between these patterns of neonatal limbic connectivity and subsequent infant behavior and cortisol reactivity. Ongoing work in this area may shed light on the etiology of sex differences in psychiatric disorders.

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Poster

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NARSAD

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Title: Maternal prenatal stress is associated with reduced fetal global neural efficiency

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Abstract: Emerging evidence supports a strong link between maternal prenatal stress and altered postnatal brain development. However, whether stress is reflected in brain development prior to birth, and specifically, whether maternal prenatal stress alters fetal functional brain systems, remains an open question. Given that neurodevelopmental disorders implicated in prenatal stress, such as autism and ADHD, are often characterized by decreased global neural efficiency and reduced network integration, we tested the hypothesis that higher levels of maternal stress would be associated with decreased global efficiency of the fetal neural connectome. The fetal neuroimaging sample consisted of 47 cases (28 male; age range 30-37 weeks), with mother mean age 25.1 years (SD 4.2). Spatially constrained group level clustering was used to parcellate the fetal brain into 197 spatially contiguous regions from which subject functional connectivity (FC) matrices were derived. Topological properties of FC matrices were then quantified by means of graph theoretical analyses. A measure of global neural communication efficiency was computed as the inverse of the average number of steps needed to travel from every region in the network to every other region in the network, with longer paths being less efficient. Nodal efficiency was obtained by computing the average inverse shortest path of that specific node to each other brain region. Permutation testing was used to compute normalized values by dividing the efficiency by the averaged efficiency of 1000 random networks with the same degree distribution. To mitigate potential influence of the threshold set for participant functional graphs (T=0.25), results were replicated with adjusted thresholds, T=0, and T=0.30. Scales from six questionnaires assessing maternal stress were best represented as single latent factor, showing high loadings and good model fit. Associations between maternal stress and fetal efficiency variables were tested in a multilevel regression model that included age and motion as covariates. We discovered that higher maternal prenatal stress was associated with reduced strength of neural efficiency (p=0.04). Nodes in the fetal graph with the strongest effects were observed in areas of the cerebellum, visual association cortex, precentral gyrus, medial temporal lobe, and medial prefrontal cortex. For the first time, we report that maternal prenatal stress exerts intrauterine programming of *in vivo* human neural functional networks. This discovery has implications for

transfer of risk via early brain programming, which may be relevant to long-term psychiatric health.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.18/D18

Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH091864

Title: Experimental manipulation of prefrontal cortex differentially affects amygdala reactivity following early-life stress

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Abstract: Early-life adversity can have profound and lasting effects on affective development and behavior. Humans rely on their caregivers longer than any other species, making parental deprivation one of the most potent stressors for an infant. Prior studies suggest that parental deprivation alters the development of frontoamygdala circuitry and related anxiety. However, the functional nature of these abnormalities is unknown. Here we manipulated prefrontal engagement via cognitive load to experimentally test its effects on subsequent amygdala reactivity during development in children who experienced parental deprivation via previous institutionalization (PI) during infancy and typically developing comparison youth (8-11 years old). At baseline (low cognitive load), there were no group differences in prefrontal engagement, but PI children showed heightened amygdala reactivity to subsequently presented faces. During high cognitive load, comparison children increased prefrontal engagement and had subsequent increases in amygdala reactivity. By contrast, PI children showed lower prefrontal activation and did not show subsequent changes in amygdala reactivity. The results suggest that early-life adversity alters later frontoamygdala development, with heightened amygdala reactivity as a baseline state and weaker prefrontal recruitment during cognitively demanding conditions. Thus,

the nature of amygdala-PFC interactions differs qualitatively between comparison and PI youth. The present findings indicate that early-life adversity alters normative development of the neural circuitry supporting emotion regulation with lasting effects on emotional behavior. Amygdala-PFC phenotypes following parental deprivation may be ontogenetic adaptations that the developing system makes to meet the demands of an adverse environment, which are likely to have long-term consequences on behavior.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.19/D19

Topic: A.07. Developmental Disorders

Title: Environmental Influences on early childhood hippocampal growth

Authors: *T. NICHOLS[1], L. M. BETANCOURT[3], P. A. YUSHKEVICH[2], L. E. M. WISSE[2], B. B. AVANTS[2], M. ASHTARI[4], H. HURT[3], M. J. FARAH[1]
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Abstract: Hippocampal development is predictive of emotional health and learning ability in humans and in animal models. Childhood hippocampal volume has been found to vary as a function of family poverty, with poor children having smaller hippocampi. How early do these effects emerge, and what environmental factors might be responsible for them? We addressed these questions with a sample of healthy term infants who underwent MRI at approximately 1 month, 1 year and 2 years of age (N at 2 years = 23, all African American females). Families ranged in SES from below the poverty line to more than 400% of the poverty line. Through multiple interviews, standardized scales, home visits and neighborhood census data we measured aspects of the children’s environments that are generally correlated with family poverty and may influence hippocampal development: COGNITIVE stimulation (e.g., language interaction, provision of books and playthings, exposure to different people and surroundings), PARENTING warmth and engagement (e.g., physical affection, disciplinary practices, positive speech) and NEIGHBORHOOD socioeconomic status (e.g., percentages of unemployment, public assistance, female-only households with children). We also measured family FINANCIAL circumstances (income-to-needs ratio and food insecurity). We were then able to perform regressions to predict 2-year hippocampal growth with the four aspects of the environment listed above, which were moderately correlated with one another but did not result in collinearity. To assess growth in relation to these influences, we covaried hippocampal

volume at 1 month. In this sample of subjects, NEIGHBORHOOD socioeconomic status was the most powerful predictor of hippocampal growth (Left hippocampus, β=.39, $p<0.0005$, right hippocampus, β=.44, p=0.008), with PARENTING warmth and engagement also predicting left hippocampal growth (β=.22, $p<0.004$). These results suggest that neighborhood characteristics, which have been linked to child and adult health over and above individual and family level socioeconomic status, are also associated with hippocampal development in the first two years of life. These data also indicate a role for parental warmth and affection in early hippocampal development, consistent with the large literature on parenting behavior and off-spring hippocampal development in animal models.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.20/D20

Topic: A.07. Developmental Disorders

Support: R01MH093677

Title: Maternal Immune Activation by C-reactive protein and neonatal connectivity of the salience network

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Abstract: During pregnancy, maternal immune activations (MIAs) arise from infection, environmental stress, and poor physical health and, in preclinical models, have proximal and long lasting impact on offspring. Translational human studies are just beginning to consider MIAs with alterations in the brain and behaviors. In infants, two studies found an association with MIAs and head circumference, an indirect measure of the brain. Epidemiological studies have associated MIAs with increased risk of psychiatric disorders. Nevertheless, there remains a paucity of human research investigating the role of MIAs in altered neurodevelopment. In contrast, numerous preclinical models investigating MIAs with rodents or non-human primates provide templates to inform human studies. MIAs have been associated with altered development in a widespread and non-specific set of brain regions including the hippocampus, the prefrontal cortex, the mid-temporal lobe, the parietal lobe, the insula, and the cingulate cortex. However, behavioral deficits are more specific to emotion, inhibition, and attention regulation. In humans, these behaviors have been related to functional connectivity patterns of

the salience network, a large-scale brain network anchored by the dorsal anterior cingulate (dACC). Together, these converging results suggest that dACC represent good candidates regions for investigations of functional connectivity patterns associated with MIAs. Here, we test the hypotheses that higher levels of MIAs as measured by maternal C-reactive protein (CRP) during the 3rd trimester would be associated with greater functional connectivity of the insula and dACC in neonates. Thirty-two pregnant women, aged 14 to 19, were recruited. At 34-37 weeks of gestation, the women underwent diagnostic evaluations and blood draws. CRP was measured using the enzyme-linked immunosorbent assay. For the neonates, resting-state functional MRI data were acquired on a GE Signa 3T scanner. Standard seed connectivity from the dACC was performed. CRP was correlated with connectivity while controlling for postmenstrual age (PMA) at scan and sex. With higher levels of maternal CRP, the neonates exhibited weaker connectivity between the dACC and mPFC. These regions are critical for performing many cognitive behaviors and are consistently implicated in neuropsychiatric disorders, suggesting a pathway for MIAs to increase psychiatric risk. Future studies should to relate MIAs and these brain regions to neurobehavioral development.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.21/D21

Topic: A.07. Developmental Disorders

Support: P30 ES023515

Title: Prenatal and early childhood exposure to neurotoxic metals and internalizing behaviors

Authors: *M. HORTON[1], L. HSU[1], B. CLAUS HENN[2], A. MARGOLIS[3], C. AUSTIN[1], K. SVENSSON[4], M. TÉLLEZ ROJO[5], L. SCHNAAS[5], C. GENNINGS[4], R. WRIGHT[1], H. HU[6], M. ARORA[1]
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Abstract: Background: Early life uptake of neuroactive metals can alter neurodevelopment outcomes, but little is known about the critical windows of susceptibility when exposure exerts the strongest effect. Most epidemiologic studies examining the neurodevelopmental effects of early life metal exposure focus on individual agents and fail to account for real-world scenarios in which humans, including the developing infant, are exposed to multiple chemicals.

Methods: Among 133 subjects enrolled in a longitudinal birth cohort study, PROGRESS, we assessed prenatal and early postnatal manganese (Mn), zinc (Zn) and lead (Pb) concentrations in children's shed teeth using laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) and behavior using the Behavior Assessment System for Children, 2nd edition (BASC-2) at 48 months. We used novel statistical methods including distributed lag models and lagged weighted quantile sum regression to identify the role of individual and mixed metal exposure timing on behavioral outcomes. Models controlled for maternal education.
Results: Individually, dentine Mn and Zn demonstrate a non-linear association with increased anxiety symptoms with adverse effects observed in the early postnatal period (from birth through 9 months). After birth, dentine Pb is linearly associated with increasing anxiety symptoms, with the association appearing to extend beyond 12 months. When the three metals are examined as a mixture, rather than individually, we observe two distinct windows of susceptibility to increased anxious behaviors; the first window (*around 4 months*) appears to be driven largely by dentine Mn while the association at the second window (*after 8 months*) seems to be driven by the mixture of the 3 metals, and dominated by Pb.
Conclusion: These results suggest that each metal (Mn, Zn and Pb) may have a postnatal window of susceptibility to behavioral outcomes, and when considering exposure to a mixture of metals, there may be unique periods of increased vulnerability. These mixture-driven associations would be missed using traditional biomarkers that do not provide fine scale temporal resolution of direct fetal exposure.

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Poster

120. Neurodevelopmental Disorders: Human Studies

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 120.22/D22

Topic: A.07. Developmental Disorders

Support: NIH Grant R01 MH093605

Title: Childhood family relationships, development of neural reward systems, and adolescent depression

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Abstract: Challenging family contexts are a potent, influential aspect of childhood social context risk, with consequences for a variety of psychopathology outcomes. For children in families with low socioeconomic status, experiences such as maltreatment, family conflict, and harsh parenting are potential mechanisms through which context can impact healthy functioning, especially through development in vulnerable brain systems (Humphreys & Zeanah, 2015). Emerging evidence indicates that family relationship risk—for example, disruptions in the mother-child relationship, such as physical abuse or low warmth— is associated with function in neural systems involved in affective and social processing. These systems continue to develop into early adulthood, creating a potential foundation for problems in later functioning. Function of reward circuitry may be particularly relevant to this line of investigation given its role in social processing, self-relevant processing, and depression. Using detailed social-context measures and fMRI in a longitudinal studies of high-risk adolescent girls, this presentation will examine the role of neural response to reward in the context of associations between early adversity and adolescent depression.

Participants were 232 adolescent girls from a community study of risk for depression who have been followed since age 5. Mothers completed measures of parenting practices, parent-child relationship quality, parent-partner conflict, family climate, and maltreatment throughout childhood. Girls completed diagnostic psychiatric interviews at ages 9-18 and underwent fMRI on a Trio 3T scanner with a monetary reward task at ages 16, 17, and 18 years. Preprocessing and analyses were conducted in SPM, multiple testing was addressed with family-wise error correction at $p<.05$, and the PROCESS macro was used to test mediation.

Exploratory factor analyses at ages 5-10 years yielded 3 early relationship factors: relationship quality, maternal involvement, and rewarding desired behavior. Relationship quality predicted age 16 mid-cingulate response to reward, rewarding behavior predicted age 16 putamen response, and superior temporal gyrus response mediated associations between rewarding behavior at age 5 and depression at age 16. In addition, from age 16-17 increasing depression was associated with increasing dorsolateral prefrontal cortex response.

Neural reward systems could be sensitive to early social-context influences, particularly in the family domain. Disruption of development in these neural systems could provide a mechanism for higher vulnerability for depression.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

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Program#/Poster#: 120.23/D23

Topic: A.07. Developmental Disorders

Support: NIEH grant P30ES023515

Title: Early-life manganese exposure and intrinsic functional connectivity of the developing brain

Authors: *E. DE WATER[1], E. PROAL[3], V. WANG[2], S. MARTÍNEZ MEDINA[3], L. SCHNAAS[3], M. TÉLLEZ-ROJO[4], R. O. WRIGHT[1], C. Y. TANG[2], M. K. HORTON[1]
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Abstract: Manganese (Mn) is an essential trace metal that is neurotoxic at high levels of exposure. Disruption of brain maturation processes during the prenatal period may have lasting consequences. During this critical period, the developing human brain is uniquely vulnerable to exposure to environmental toxicants such as Mn, and prenatal Mn exposure has been associated with changes in brain areas involved in emotion processing and regulation. The goal of the present study was to examine whether prenatal Mn exposure is associated with changes in the intrinsic functional connectivity (iFC) of the brain in childhood, focusing on changes in emotional brain areas. In this pilot study, 20 subjects (11 girls; aged 6-7 years) were selected from an ongoing longitudinal birth cohort study to participate in a resting state functional magnetic resonance imaging (fMRI) study. Prenatal Mn exposure was determined from maternal blood collected during the 2nd and 3rd trimesters of pregnancy. We used seed-based correlation analyses to examine whether prenatal Mn exposure was associated with the iFC of the brain in children. We selected 4 seeds from the Harvard-Oxford Cortical atlas: bilateral ACC, bilateral middle frontal gyrus, bilateral insula, bilateral superior parietal lobule; and 2 seeds from the Harvard-Oxford Subcortical atlas: right and left pallidum. Analyses were Bonferroni-corrected for the number of seeds ($Z>2.3$, FWE-corrected $p<.0083$).
We found that the bilateral anterior cingulate cortex and right pallidum showed reduced iFC with medial and lateral prefrontal areas in children who were exposed to higher prenatal Mn levels. The right pallidum findings were particularly robust, in that they remained significant after controlling for sociodemographic (child sex, SES, maternal education, home environment support) and environmental (prenatal lead exposure, air pollution) confounders. These findings indicate that prenatal Mn exposure is associated with reduced iFC of brain areas involved in emotion processing and regulation in children. Future studies should investigate whether this reduced iFC mediates the association between prenatal Mn exposure and emotional dysfunction in childhood.

Disclosures: E. De Water: None. **E. Proal:** None. **V. Wang:** None. **S. Martínez Medina:** None. **L. Schnaas:** None. **M. Téllez-Rojo:** None. **R.O. Wright:** None. **C.Y. Tang:** None. **M.K. Horton:** None.

Poster

120. Neurodevelopmental Disorders: Human Studies

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National Institutes of Health, Grant/Award Number: 5R01HD078561-04

Title: Quantitative analysis of cerebral cortex in patients with brain malformations

Authors: *L. VASUNG[1], J. LEVMAN[3], A. C. EVANS[4], E. TAKAHASHI[2]
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Abstract: During prenatal development, the human brain undergoes significant morphological changes. Specifically, during this period, primary and secondary convolutions of cerebral cortex start forming. Although prenatal development is marked by series of neurogenic events, it is still unknown which one of these contributes the most to the morphological changes in the cerebral cortex (e.g. surface area, cortical thickness, and local gyrification index). In order to answer this question, we quantitatively analyzed the cerebral cortex of patients with malformations and compared these metrics to those of healthy controls.
After the local ethical committee approval, we retrieved radiological reports from Boston Children's Hospital (BCH) radiological database using the following keywords: polymicrogyria, agenesis of corpus callosum, and thinning of corpus callosum. Reports consisted of patients at BCH between 2008 and 2016. All radiological reports were retrospectively reviewed. Patients that had a cerebrovascular disease or underwent a neurosurgical intervention were excluded from this study. In total, we included 118 patients (agenesis of corpus callosum or corpus callosum thinning (N=66), polymicrogyria with agenesis or corpus callosum thinning (N=21), and polymicrogyria (N=31). Sixty-one percent of the patients were males. The mean age of the patients at their MRI scans was nine years (mean=9.2, SD=6.5). Eighty-five percent of MRI examinations were selected after a quality control of structural T1-weighted MR images. In order to have a control group, we included 150 patients from the same database that did not have brain pathology as reported by experienced neuroradiologists.

MR images were uploaded to the CBRAIN platform (https://portal.cbrain.mcgill.ca) and were processed using the CIVET 2 pipeline (http://www.bic.mni.mcgill.ca/ServicesSoftware/CIVET). Afterwards, a second quality control was performed on the CIVET output files. Unsatisfactory results of brain segmentation were manually corrected, and the CIVET 2 pipeline was reapplied to data with corrected segmentations. Regional cortical thickness and surface area, gyrification index, and regional cortical volume were extracted for each patient. These metrics were compared between patients with polymicrogyria and controls, patients with agenesis or thinning of the corpus callosum and controls, and between patients with polymicrogyria with thinning or agenesis of the corpus callosum and controls.
To our knowledge, this is the first study determining which quantitative parameters of the cerebral cortex are altered the most in patients with different brain malformations.

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Poster

120. Neurodevelopmental Disorders: Human Studies

Location: Halls A-C

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Program#/Poster#: 120.25/D25

Topic: A.07. Developmental Disorders

Title: Two patients showed junctional neural tube defect

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Abstract: Background and purpose Primary and secondary neurulation are the two known processes that form the central neuraxis of vertebrates. Recently, a separate neurulation process in the transition zone between primary neural tube and secondary neural tube is reported which is called junctional neurulation. Defects in this process is extremely rare and only a few cases were reported. We report two cases of suspected junctional neural tube defects that required surgery recently.
Case Summary One case was a 6-month-old female presented with lower extremity weakness. Segmental narrowing of the spinal cord at T7-12 and segmentation anomalies in T9-S4 vertebrae with severe spinal canal stenosis at T10-L1 level was noted on computed tomography and MRI of the spine. Surgical decompression with filum section was done with intraoperative monitoring. The other was a 7-year-old female who had underwent surgery for ‘untethering’ and spinal deformity at other hospitals. She had severe lower extremity spasticity including bladder which resulted in renal damage. MRI of the spine revealed that the spinal cord tapers from the T8 level and becomes thick again at the lumbar level. Sacral dorsal rhizotomy with selective motor rhizotomy was performed to decrease bladder tone successfully.

Conclusion We report two cases of junctional neural tube defect which is suggested recently. Clinical features and electrophysiologic findings do not seem to show normal connections between the primary neural tube and the secondary neural tube.

Disclosures: K. Wang: None. **J. Lee:** None. **S. Chong:** None. **J. Lee:** None. **S. Kim:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

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Program#/Poster#: 121.01/D26

Topic: A.09. Adolescent Development

Support: Ministry of Science, Education, Culture and Sports of Japan (Grant Number 15K10512)

Title: Intravenous anesthetic-induced neurotoxic shift with age in the developing periods

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Abstract: General anesthetics are indispensable for not only surgery but sedation for neonates, infants and children. However, increasing evidences from animal studies suggest that exposure to anesthetics induces neurotoxicity in the developing brain, raising concerns regarding the safety of general anesthesia for young patients. In the present study, using morphological examinations *in vitro*, we aimed to determine whether anesthetics-induced neurotoxicity vary according to the different stages of day *in vitro* (DIV) in primary cultured cerebral cortical neurons. Primary cerebral cortical neurons from E17 rats were used. The neurons were exposed to intravenous anesthetics; propofol (PPF), thiopental sodium (TPS) or midazolam (MDZ) on 3, 7 or 13 days *in vitro* (DIV) for 24 hr, respectively. The survival rate of neurons was evaluated on photomicrographs before and after exposure to an anesthetic. On DIV 3-4 experiments, while TPS (100μM) and MDZ (10μM) did not attenuate the survival rate of neurons significantly, MDZ (100μM) and PPF (10 and100μM) elicited neuronal death compared to vehicles, respectively. On DIV 7-8 experiments, neither TPS (100μM), MDZ (10, 100μM) nor PPF (10μM) killed neurons significantly, while PPF (100μM) elicited neuronal death compared to vehicles. No anesthetics elicited neuronal death compared to vehicles on DIV 13-14 experiments. These results suggested that PPF- and MDZ-elicited neurotoxicity might be alleviated with according to the progress of DIV, while TPS did not show neurotoxicity at any stage.

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Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.02/D27

Topic: A.09. Adolescent Development

Title: Sex-differences in, and neural correlates of, social preference behavior in older adolescent rats

Authors: H. C. SKINNER[1], S. L. SANTIAGO[1], M. PAVELKA[2], L. B. BUCHANAN[1], D. I. ALEWEL[1], R. C. PIERCE-MESSICK[1], B. A. BARKER[1], *M. C. ZRULL[1]
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Abstract: Adolescence is a time of rapid growth and increased propensity for exploring and learning about one's environment. Often, increased interest in novelty, including how adolescents interact with conspecifics, can lead to risk taking. Environmental enrichment (EE), exposing an animal to a novel and enhanced environment on a regular basis, can affect social preference (SP) with EE modulating SP by influencing adaptability in novel situations. We investigated the impact of EE on SP in adolescent rats. Long-Evans female (n=6) and male (n=6) were exposed to EE for 1.5-h 18 times between postnatal days (pnd) 21 and 49. Age and sex matched controls (n=12) were held twice on those 18 days. On pnd 49, rats performed a SP tasks that involved placing a rat in an open field with one (Trial 1) or two (Trial 2) stimulus rats. Trial 1 was a sample trial, and after a 30-min delay, Trial 2 occurred with one familiar and one novel stimulus rat. The proportion of initiated contacts and time spent with the novel stimulus rat on Trial 2 was of interest. Neural activity evoked in basolateral amygdala (BLA) and CA2 of the hippocampus via Trial 2 of the SP task was examined using immunohistochemistry for the c-FOS protein. On Trial 2, male EE rats initiated contact with the novel stimulus rat 85% more often than female EE rats (p<.02), but male and female control rats initiated similar contacts with the novel stimulus rat. While male and female EE rats spent similar proportions of time interacting with the novel stimulus rat, control male rats spent 52% more time with the novel stimulus rat than female controls (p<.01). FOS+ neuron densities indicated EE rats showed less SP task evoked activity in BLA (-60%, p<.01) and CA2 (-60%, p<.01) than control rats. Behavioral data show EE males have a tendency to initiate more contact than EE females with a novel conspecific while control males and females show similar contact initiation, which may result from EE influencing maturational sex differences. EE does seem to mediate time spent with an unfamiliar conspecific for both males and female possibly by altering adaptation to novelty relative to controls. Reduced BLA activation in EE animals supports the idea that enrichment can reduce anxiety, stress and other emotional responses. Similarly, reduced activation of CA2 in EE rats may be due to enrichment facilitating efficiency within the hippocampus, so less activation of this circuitry would be needed to engage in social recognition

based in memory. These results offer possible neural correlates for the observed balance in time spent with novel and familiar conspecifics by EE rats.

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Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

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Program#/Poster#: 121.03/D28

Topic: A.09. Adolescent Development

Support: Australia National Health and Medical Research Council (NHMRC) Project Grant (APP1104184)

Australia National Health and Medical Research Council (NHMRC) Peter Doherty Fellowship (APP1125937)

Title: Effects of early antipsychotic drugs exposure on binding density of NMDA and GABAA receptors in juvenile rats

Authors: *J. LIAN, C. DENG
Univ. of Wollongong, Wollongong, Australia

Abstract: Background: Antipsychotic drugs were developed to treat schizophrenia in adults; however they have been increasingly prescribed in children and adolescents, without understanding the underlying mechanisms. Adolescence is a critical period in neurodevelopment, where the brain undergoes many structural reorganisations before stabilising towards adulthood. The glutamatergic NMDA and GABAA receptors are involved in neurodevelopment and various brain functions, as well as the pathophysiology of a range of childhood mental disorders, such as anxiety, depression, child-onset schizophrenia and other behavioural disorders schizophrenia. This study investigated whether early treatment of risperidone, olanzapine and aripiprazole (three widely-used antipsychotics in children and adolescents), affect NMDA and $GABA_A$ neurotransmission in juvenile rats.
Methods: Male and female Sprague Dawley rats treated orally three times per day with risperidone (0.3 mg/kg, t.i.d.), olanzapine (1 mg/kg, t.i.d.), aripiprazole (1 mg/kg, t.i.d.), or vehicle (control) starting from postnatal day (PD) 23 (±1 day) for 3 weeks (a period corresponding to the childhood-adolescent period in humans). Quantitative autoradiographic methods were used to detect the binding density of [^{3}H]MK-801 (a NMDA receptor antagonist) and [^{3}H]muscimol (a selective $GABA_A$ receptor agonist).
Results: Risperidone treatment significantly decreased the [^{3}H]MK-801 bindings in the

prefrontal cortex (PFC), nucleus accumbens core (NAcC), and caudate putamen ($p<0.05$), as well as cingulate cortex (Cg) and nucleus accumbens shell (NAcS) of rats ($p<0.01$). Olanzapine significantly reduced the NMDA receptor (NMDAR) binding levels on NAcS ($p<0.01$), Cg and CPu ($p<0.05$). Aripiprazole slightly enhanced NMDAR binding level in Cg and PFC (both $p=0.051$). In terms of the female rats, aripiprazole treatment slightly increased the NMDAR binding density in NAcS ($P=0.053$), while risperidone treatment significantly elevated the NMDAR binding density in NAcC ($p<0.05$), CPu ($p<0.01$), and slightly increased the NAcS and PFC (both $p=0.055$). Aripiprazole tended to increase the $GABA_A$ receptor binding density in the PFC ($p=0.078$). However, olanzapine and risperidone have no effect on the $GABA_A$ receptor binding level in other brain regions in both genders.
Discussion: These results suggest that early treatment of these antipsychotics affects glutamatergic NMDA and GABAergic $GABA_A$ neurotransmission in juveniles, which may play a role in their clinical efficacy in the control of mental disorders, such as anxiety and child-onset schizophrenia in children and adolescents.

Disclosures: J. Lian: None. **C. Deng:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Health and Medical Research Institute (NHMRC) Project Grant.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.04/D29

Topic: A.09. Adolescent Development

Title: Effects of bisphenol-A and estrogen exposure during adolescent development on behaviors and dendritic spine density in adulthood

Authors: *R. E. BOWMAN[1], J. HAGEDORN[1], E. MADDEN[1], M. FRANKFURT[2]
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Abstract: Bisphenol-A (BPA) is an endocrine disrupter that exerts effects on a variety of neural, physiological, and behavioral measures. We have recently shown that BPA exposure, in adolescent gonadally intact rats, increases anxiety, impairs spatial memory, and decreases dendritic spine density when measured in adulthood (Bowman et al, 2014, 2015). Additionally, estrogen (E) is neuroprotective, enhances memory, and increases dendritic spine density; however, E replacement studies in adolescence are limited. Thus, this experiment examined the effects of adolescent BPA exposure in juvenile rats under controlled hormone conditions on behavioral and neural alterations in adulthood. Female Sprague-Dawley rats were ovariectomized at postnatal day (PND) 21 and received subcutaneous injections of either BPA

(40 µg/kg/bodyweight), E (50 µg/kg/bodyweight), or oil during adolescence (PND 38-49). Starting PND 77, subjects were tested for anxiety (elevated plus maze), spatial memory (object placement), and non-spatial visual memory (object recognition). Animals were sacrificed at 13 weeks and brains processed for Golgi impregnation. Adolescent hormone treatment significantly altered body weight gain across time and BPA animals weighed more than E subjects. Surprisingly, there were no significant group differences on any of the behavioral measures. Dendritic spine density in pyramidal cells in the CA1region of the hippocampus, granule cells of the dentate gyrus and pyramidal cells in the medial prefrontal cortex is being assessed. Past studies have used gonadally intact adolescent rats and the results of the current study provide an initial examination of the extent to which previously observed effects are due to the BPA exposure versus natural fluctuations in gonadal hormones.

Disclosures: R.E. Bowman: None. **J. Hagedorn:** None. **E. Madden:** None. **M. Frankfurt:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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PIP-CONICET 00323

Title: Changes of hippocampal oxidative status in immature rats exposed to noise: influence of elapsed time after exposure and environmental stimulation

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Abstract: Previous studies of our laboratory showed that exposure of immature rats to moderate noise can induce hippocampus (HC)-related behavioral, biochemical and histological alterations during the peri-adolescence period. In addition, rearing animals in an enriched environment (EE) has shown to be effective in the reversal of most behavioral alterations. However, comparative data of HC oxidative levels at different post-exposure ages were not obtained yet. Thus, the aim of the present work was to test the potential differences in HC oxidative status of rats exposed to noise at an early developmental age as well as the possible reversal of these changes by rearing

in an EE for different periods. Male Wistar rats of 7 days were exposed for 2 hours to white noise (95-97 dB). After weaning, groups of 3-4 rats were transferred to an enriched cage, consisting of different toys, a wheel, plastic tunnels and ramps. Other groups were placed in standard cages. One or two weeks later, levels of Trx1 -an antioxidant of the thioredoxin family- were tested through Western blot experiments. Results showed that Trx-1 levels were increased in exposed animals one week after weaning, when compared with non-exposed rats. However, rearing animals in an EE was effective in restoring these differences. In contrast, when Trx-1 levels were tested two weeks after weaning, there were no significant differences in Trx-1 levels, neither in standard nor in enriched conditions. These findings suggest that an oxidative imbalance might be triggered after noise exposure that can be observed at least until three weeks after exposure. Nevertheless, as development continues, this parameter seemed to return to control values, suggesting that increasing age might compensate for antioxidant system dysfunction. On the other hand, whereas visual, social and physical stimulation during development seemed to be an effective strategy to reverse noise-induced changes three weeks after exposure, it resulted unsuccessful in more mature animals, even if EE was extended for two weeks. Therefore, it could be hypothesized that this intervention should operate only when an injurious agent is present. Together, these findings suggest that a narrow window of opportunity might exist, in which an environmental intervention such as EE might be effective.

Disclosures: **S.J. Molina:** None. **F. Capani:** None. **L.R. Guelman:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Topic: A.09. Adolescent Development

Support: NIH Grant AA024890

Title: Kappa opioid receptor activation dose-dependently increases anxiety-like behavior in male adolescent and adult Sprague-Dawley rats

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Abstract: Anxiety is prevalent across ontogeny, but there is evidence that its etiology may differ at various developmental stages. The amygdala is central to the production of an anxiety response, and anxiety is thought to be the result of an imbalance of excitatory and inhibitory neurotransmission in this brain region. This balance is modulated by a number of neurotransmitter systems, including the opioid system. The kappa opioid receptor (KOR) system in particular has been repeatedly implicated in mediating aversive responses to environmental

stimuli. However, recent evidence has revealed that KOR function in the basolateral amygdala (BLA), the amygdalar nucleus known to initiate the anxiety response, is developmentally regulated. Specifically, it has been shown that KOR activation increases GABA transmission in adolescents, but not in adults. This supports the few studies that have shown anxiolytic effects of KOR activation in younger animals, findings which are contrary to the anxiogenic effects reported in older animals. However, despite the apparent discrepancy in KOR function, a direct comparison of KOR-induced anxiety in adolescents and adults has not been previously done. Similarly, little is known about the impact of KOR activation in females regardless of age. Therefore, we assessed the effects of KOR-induced anxiety-like responding in adolescent and adult male and female Sprague-Dawley rats on the elevated plus maze following i.p. injections of the synthetic KOR agonist U69593 (U69593; 0.01, 0.1, or 1 mg/kg). We found that adolescent males displayed significantly more anxiogenic behavior only with the lowest dose (0.01 mg/kg) and only during the first 2 minutes of testing. Conversely, adult males displayed greater anxiogenic behavior only at our highest dose (1 mg/kg) and also only during the first 2 minutes of testing. Interestingly, females seemed to be resistant to KOR-induced anxiety, with adolescents showing no changes at any dose of U69593 and adults showing a reduction in anxiety-like behavior at 1 mg/kg across the entire testing period. The discrepancy between our results and those of recent electrophysiological reports suggests that, in adolescent males, the opposing function of amygdalar nuclei may be overriding the effects of the BLA to produce anxiety-like behavior similar to that seen in adults. However, our finding of developmental and sex differences in sensitivity to KOR-induced anxiety is novel, and should be explored further.

Disclosures: **K. Przybysz:** None. **Y. Valentine:** None. **M. Diaz:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Title: Effects of neonatal caffeine exposure on locomotor activity in adolescent rats: Role of methylphenidate pretreatment

Authors: *R. MEHTA[1], T. SANVICTORES[2], A. R. ZAVALA[2]
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Abstract: Chronic neonatal caffeine exposure increases locomotor activity later in life. This caffeine-induced hyperactivity is dependent on the age of initial exposure, as only pretreatment during postnatal days (PDs) 7-11 resulted in hyperactivity in adolescent (PD 25) and adult (PD 60) rats, whereas exposure to caffeine during PD 13-17 had no effect in adult rats or resulted in hypoactivity in adolescent rats. To date, the effect of administering methylphenidate to rats exposed to caffeine during the neonatal period has not been examined. Thus, the present experiment examined whether neonatal caffeine exposure produces hyperactivity in adolescence rats, as well as determine if methylphenidate pretreatment can alter this effect. Beginning on PD 7, male and female rats were pretreated with either saline or 20 mg/kg of caffeine for seven consecutive days (i.e., PD 7-13). Horizontal locomotor activity was then assessed from PD 25-28, followed by five consecutive days (i.e., PD 29-33) during which rats were pretreated with saline or methylphenidate (2.5 or 5 mg/kg). Results show that neonatal caffeine exposure produced hyperactivity in adolescent rats and that the effect was modulated by methylphenidate pretreatment in a dose-dependent manner. These findings suggest that neonatal caffeine exposure during PD 7-13 may serve as a potential model to study the etiology of Attention Deficit Hyperactivity Disorder (ADHD).

Disclosures: R. Mehta: None. **T. Sanvictores:** None. **A.R. Zavala:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Topic: A.09. Adolescent Development

Support: SC2GM109811

Title: Juvenile exposure to fluoxetine induces an enduring anxiogenic-like behavioral profile in female c57bl/6 mice

Authors: *F. J. FLORES RAMIREZ, I. GARCIA, S. A. CASTILLO, T. G. MIRAMONTES, M. ARENIVAR, J. PRECIADO-PINA, S. D. INIGUEZ
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Abstract: Accumulating preclinical evidence indicates that early-life exposure to psychotropic medications results in altered behavioral responses to stress in adulthood. However, to date, these preclinical experimental approaches have been conducted primarily using male subjects. This is surprising given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, to be prescribed with psychotropic medications such as antidepressants. Therefore, to examine if altered sensitivity to anxiety-inducing situations are exhibited in adulthood, as a result of juvenile exposure to antidepressants, we exposed adolescent

female c57bl/6 mice to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX). We selected FLX given that it is the only SSRI approved by the US Food and Drug Administration for the treatment of pediatric depression. Specifically, female mice were forced to consume FLX in their drinking water (250 mg/L) from postnatal day [PD]-35 to PD49, and were later assessed in adulthood (PD70+) on responsivity to the elevated plus-maze and the light-dark box test - traditional behavioral paradigms used to assess anxiety-like responses in rodents. Our results show that adult female mice pretreated with FLX during adolescence spent less time in the open arms of the elevated plus-maze, when compared to saline-pretreated controls. Similarly, when tested on the light-dark box, FLX-pretreated mice displayed significantly longer latencies (sec) to enter the light-side compartment of the testing chamber, and spent significantly less time (sec) within this compartment, when compared to controls. No differences in locomotor activity were evident between the groups as a function of SSRI pre-exposure. Collectively, our data suggest that adolescent exposure to FLX mediates behavioral adaptations that endure into adulthood, which are indicative of a generalized anxiogenic-like phenotype, in female mice.

Disclosures: **F.J. Flores Ramirez:** None. **I. Garcia:** None. **S.A. Castillo:** None. **T.G. Miramontes:** None. **M. Arenivar:** None. **J. Preciado-Pina:** None. **S.D. Iniguez:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Topic: A.09. Adolescent Development

Support: SC2GM109811

Title: Effects of ketamine and chlordiazepoxide on social behavior after vicarious defeat stress exposure in female c57BL/6 mice

Authors: I. GARCIA, S. A. CASTILLO, D. O. SANCHEZ, F. J. FLORES-RAMIREZ, *S. D. INIGUEZ
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Abstract: Stress exposure is a risk factor for the development of mood-related illnesses, such as anxiety and major depressive disorder (MDD). Despite the growing literature suggesting that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains to be thoroughly examined at the preclinical level. Thus, the objective of the current investigation is to assess if the vicarious defeat stress (VDS) behavioral paradigm, a model of psychological stress, decreases social behavior in female c57BL/6 mice. Also, to examine whether pharmaceuticals used to treat MDD (ketamine) and anxiety (chlordiazepoxide) would reverse the VDS-induced behavioral profile observed. To do this, female mice vicariously

experienced the social defeat bout of a male conspecific, by a larger CD1 male aggressor, for 10 consecutive days (10-min per day). After the last stress exposure, experimental mice were single-housed and administered with saline, ketamine (20 mg/kg), or chlordiazepoxide (10 mg/kg). The following day, mice were tested in the social interaction test. Our results show that when compared to non-stressed controls, female mice exposed to VDS displayed lower interaction ratios. Furthermore, our results indicate that ketamine and chlordiazepoxide, respectively, reversed the decreases in social behavior as a function of VDS, without altering general locomotor activity. Collectively, our data suggest that both ketamine and chlordiazepoxide may alleviate the social dysfunction associated with psychological stress-induced disorders in female populations.

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Poster

121. Animal Models: Impact of Environment on the Brain

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Topic: A.09. Adolescent Development

Title: Mutually experienced stress during adolescence buffers against social defeat-induced avoidance in physically stressed mice

Authors: *L. F. ALCANTARA[1], J. ROZOFSKY[2], O. K. SIAL[2], C. A. BOLANOS-GUZMAN[2]
[1]Texas AM: Psychology, College Station, TX; [2]Psychology, Texas A&M Univ., College Station, TX

Abstract: Individuals who are emotionally, physically, or sexually abused as children have a higher prevalence of major depression, drug abuse, and suicide. It has been shown that participation in youth programs can be beneficial to adolescents who experience trauma, suggesting that social support is important in promoting resiliency to stress. Our previous work using the vicarious social defeat stress (VSDS) paradigm demonstrated that repeatedly witnessing a conspecific being physically overpowered can lead to social avoidance and both, short- and long-term deficits in mood-related behaviors. Although various pharmacological interventions can reverse or buffer against some stress-induced deficits, having social support may be beneficial in attenuating future maladaptive behaviors. Given that social structure is crucial during formative years, it is important to determine if in the VSDS model, addition of a social buffer is capable of buffering stress and/or promoting resilience. To this end, we ran a modified VSDS paradigm between postnatal days (PD) 35-44 in which each physically-stressed (PS) mouse was paired to the same VSDS-exposed mouse (witness) throughout the entirety of the defeat (10 days). An additional cohort of paired mice went through VSDS, however, at the

time of defeat the witness mouse was taken out of the cage and returned after the defeat bout (non-observer). This approach was taken in order to assess whether mutually experiencing the stress of defeat would change the potential of a cagemate to provide a buffer to the stressful experience of the mouse in the PS condition. All mice were then tested in the social interaction test (SIT) 24 hours after the last defeat bout. PS-exposed mice that had a cagemate witness the defeat showed significantly less avoidance to both a novel CD-1 aggressor and a novel C57 social targets when placed in the SIT arena. Surprisingly, both the witness and non-observer cagemate groups showed avoidance to a CD-1. PS-exposed mice without a cagemate mutually experiencing the defeat showed avoidance to both novel social targets. Additionally, just witnessing stressful events, or being housed with a stressed cagemate induced avoidance in the non-stressed cagemates. Taken together, this data suggests that mutual experience may be an important component of social buffering for mice exposed to stress. Furthermore, using different housing or cagemate conditions may yield varying results in avoidant behavior, and further experimentation is necessary.

Disclosures: L.F. Alcantara: None. **J. Rozofsky:** None. **O.K. Sial:** None. **C.A. Bolanos-Guzman:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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NIH Grant 8RL5GM118978-03

Title: Sex differences in oxycodone-induced conditioned place preference in early adolescent male and female rats

Authors: *A. T. MANOOGIAN[1], Y. C. BROWN[2], A. R. ZAVALA[3]
[1]Psychology, California State Unviersity Long Beach, Los Alamitos, CA; [2]Psychology, California State University, Long Beach, Long Beach, CA; [3]Psychology, California State Univ., Long Beach, CA

Abstract: Oxycodone abuse among adolescents has increased in recent years. Surprisingly, little preclinical research has been done to establish the effects of oxycodone in this period of development. We examined the rewarding effects of oxycodone in male and female adolescent rats using the established conditioned place preference (CPP) paradigm. Male and female rats

were assessed for oxycodone-induced CPP using a 10-day CPP procedure beginning on postnatal day (PD) 27. During pre-conditioning and post-conditioning sessions, rats were tested for their baseline and final place preference, respectively, in 15-min sessions. During conditioning (PD 28-35), rats underwent daily 30-min sessions, during which they received alternating oxycodone (0, .01, .04, .11, .33, 1, 3, 9 mg/kg) and saline injections in distinct compartments. Results indicated that rats showed a significant shift towards the oxycodone-paired compartment at the higher doses, with males requiring a lower dose than females to show a significant shift for the oxycodone-paired side. This data suggests that sex differences in oxycodone reward are evident early in adolescence and that there is a need to understand the neurobiology of oxycodone abuse in adolescence.

Disclosures: **A.T. Manoogian:** None. **Y.C. Brown:** None. **A.R. Zavala:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Title: SB224289, a 5-HT_{1B} receptor antagonist, decreases the aversion of nicotine in male, but not female adolescent rats

Authors: D. FRANCO[1], B. SALINAS[1], K. HERNANDEZ[1], N. S. PENTKOWSKI[2], R. A. CABRERA[1], *A. R. ZAVALA[1]
[1]Psychology, California State Univ., Long Beach, CA; [2]Psychology, Univ. of New Mexico, Albuquerque, NM

Abstract: Activation of 5-HT_{1B} receptors modulates the rewarding effects of cocaine, methamphetamine, and alcohol. To date, the role of 5-HT_{1B} receptors in the rewarding effects of nicotine has not been investigated. To identify if these receptors play a role in nicotine reward, we examined the effects of SB224289, a selective 5-HT_{1B} receptor antagonist, on nicotine reward using the conditioned place preference (CPP) paradigm-a validated animal model of drug reward. Specifically, female and male adolescent rats were conditioned on postnatal day 29-36 with saline or nicotine (0.0, 0.0022, 0.067, or 0.2 mg/kg, subcutaneously) on alternating days over an 8-day CPP conditioning procedure. During nicotine conditioning days, rats were administered SB224289 (0 or 5 mg/kg, intraperitoneally) 60 min prior to nicotine injections.

Results indicate that inactivation of 5-HT_{1B} receptors with SB224289 reduced the aversive effects of nicotine in male rats given the highest dose of nicotine (0.2 mg/kg), as these rats continued to exhibit nicotine-induced CPP, whereas rats pretreated with vehicle no longer showed CPP. In contrast, SB224289 did not affect the nicotine-induced CPP exhibited by females. Altogether, these results indicate that 5-HT_{1B} receptors play a critical role in the effects of nicotine in male rats and further suggest that 5-HT_{1B} receptors are a novel target for nicotine dependence.

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Poster

121. Animal Models: Impact of Environment on the Brain

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Program#/Poster#: 121.13/D38

Topic: A.09. Adolescent Development

Title: Task novelty influences an enrichment by sex effect on object in place task performance in adolescent rats

Authors: *H. JOHNSON[1], M. PAVELKA[2], S. L. SANTIAGO[3], D. I. ALEWEL[3], C. A. PEGGS[3], D. E. COBB[4], M. C. ZRULL[3]
[2]Psychology & Cell/Molecular Biol., [3]Psychol, [1]Appalachian State Univ., Boone, NC; [4]Program in Neurosci., Univ. of Maryland-Baltimore, Ellicott City, MD

Abstract: Enrichment experience (EE), such as repeated exposure to an enhanced environment often featuring novel objects, obstacles to navigate, and novel conspecifics, allows for investigation and informal learning that can lead to brain changes and alter novelty seeking and exploratory behaviors. For adolescent rats, performing a novel task to measure behavior can enhance novelty-seeking and be enriching. We investigated EE's impact on performance of an Object in Place (OiP) task in older, postnatal day (pnd) 49 adolescent rats and compared results to a prior study from our lab, in which OiP performance was examined at pnd 35 and 49, to determine whether effects were dependent on age or task novelty. Adolescent Long-Evans rats (6 male, 6 female) were exposed to EE between pnd 25 and 48. Sex and age-matched controls (*n*=12) experienced a non-enriched home-cage. Two-trial OiP testing occurred on pnd 49 with two delays (15 and 60 min) in an open field containing four objects. Exploration time and the time in contact with the rearranged objects were measured at each delay. After testing, brain tissue was processed to examine levels of neural activity in dentate gyrus (DG), CA1, and basolateral and lateral amygdala (BLA, LA) using immunohistochemistry for *c-fos* activation. Across delays, current pnd 49 female spent less time with rearranged objects than male EE rats (-12%), but female control rats spent more time with moved objects than male controls (+16%,

p<.05). These results parallel behavior of younger, pnd 35 EE and control rats from our previous work (-8%, +18%, *p*<.05), and while pnd 49 data from the prior data showed a similar pattern, there were no statistically significant differences in task performance across EE and sex at pnd49. Behaviorally, EE and sex jointly modify OiP performance based on task novelty. OiP task performance evoked less FOS+ neurons in CA1 (-31%, *p*<.05) and DG (-35%) of EE brains than in controls, and there was less neural activation in BLA (-17%) and LA (-51%) of EE brains relative to controls. Reduced activation of DG and CA1 suggest being enriched may lead to hippocampal processing efficiency. While the reduced LA activity in EE rats may reflect being accustomed to emotion-evoking novelty in an environment, the lack of statistically different extent of active BLA neurons between EE and not enriched brains warrants further investigation. Overall, EE appears to affect male and female adolescent rats' response to new placement of familiar environment features differently but dependent of novelty of that space.

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Poster

121. Animal Models: Impact of Environment on the Brain

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Support: NIAAA R01 AA021775

Title: Adolescent binge ethanol exposure alters specific forebrain cholinergic cell populations and results in cognitive flexibility deficits

Authors: *G. M. FERNANDEZ, L. M. SAVAGE
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Abstract: Early adolescent exposure to high ethanol (EtOH) levels leads to a reduction in forebrain cholinergic neurons and hippocampal neurogenesis. Following an adolescent intermittent ethanol exposure model (AIE; 20% EtOH v/v, 5 g/kg, 16 intragastric gavages, P25-55), functional cholinergic release was assessed during a spatial memory task (spontaneous alternation) in adulthood (P80). Both control and AIE rats had similar rates of spontaneous alternation, and there were no differences in acetylcholine release within the hippocampus during behavior. However, behaviorally- related acetylcholine release was reduced in the prefrontal cortex of AIE rats, compared to controls. Coinciding with reduced prefrontal cholinergic functioning in AIE rats, EtOH- treated rats were impaired during the first attentional set shift on an operant set-shifting task. We hypothesize these effects are mediated by a selective reduction (50%) in choline acetyltransferase (ChAT) positive neurons that were also nestin positive in the

Nucleus Basalis of AIE rats. We also found a 30% reduction in ChAT+/nestin- cells within the medial septum/diagonal band, although no AIE- mediated effect on spatial memory was detected. Doublecortin (DCX) staining, a marker offor newly born neurons, was also reduced (32%) in the dorsal dentate gyrus of AIE rats, indicative of an EtOH- mediated reduction in neurogenesis. Loss of DCX staining negatively correlated with low prefrontal cholinergic acetylcholine release during behavior and poor performance on the first cognitive set shift. Loss of DCX staining, along with reduced ChAT+/nestin+ cell populations in the Nucleus Basalis, correlated with high blood ethanol content. These results indicate that early adolescent binge EtOH exposure leads to a long-lasting hypofunctionality of frontocortical cholinergic release thatthe frontocortical-hippocampal interactions that leads to impairments in cognitive flexibility during adulthood. These effects are driven by a loss of ChAT+/ nestin+ neurons in the nucleus basalis and a reduction in dorsal hippocampal neurogenesis.

Disclosures: G.M. Fernandez: None. **L.M. Savage:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

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Title: Different types of environmental enrichment produces distinctive synaptic profiles in adolescent rats

Authors: *R. A. JEFFREY, P. GABRIEL
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Abstract: The teenage brain is looked at so often as a black box in the neuroscience world. With different experiences brains are constantly changing, but our understanding remains incomplete as to what mechanisms shape adolescent plasticity. Following activity at the synapse cellular processes required for growth, stabilization, and plasticity form a complex molecular signature. Environmental enrichment (EE) is one experimental manipulation that induces changes in the synaptic landscape of the brain. However, it is important to distinguish between the different components of enrichment (physical activity, social engagement) as studies have shown divergent results from the different experimental interventions. In this study, we have four separate groups of rats with different types of enriched environments presented during the adolescent period. Males and females were used and results were analyzed by sex. One group experienced social housing along with access to exercise equipment for rats (SE/PE), one group only had access to exercise equipment - physical enrichment (PE), one group only had access to

social enrichment (SE), and our controls were in standard housing. Analysis of social behavior and vocalizations, followed by ex-vivo analysis of synapse type, number, and biochemical composition were compared across the four groups. Our preliminary results indicate that there is an effect of our enrichment intervention during the adolescence period, specifically in social interaction and vocalizations. Additionally, we see variation in D2 dopamine receptors expression at the synapse between groups. Altogether, our results suggest differing effects of physical and social enrichment during the adolescent period, consistent with other work supporting an important role for enriched environment in synaptogenesis, neurogenesis, synapse development and cognition. Further, these changes stemming from social and physical enrichment during adolescence are not always consistent with effects of EE during adulthood.

Disclosures: R.A. Jeffrey: None. **P. Gabriel:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.16/D41

Topic: A.09. Adolescent Development

Title: Enrichment reduces hippocampal activity evoked by an object in place task in adolescent rats

Authors: *M. PAVELKA[1], R. SALINAS[2], M. C. ZRULL[2]
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Abstract: Enriching experiences can impact the structure and function of neurons and neural circuits and subsequently behavior mediated by the activity of those cells and networks. Specifically, for adolescent animals, the interaction with novel objects and same-sex conspecifics, or environmental enrichment (EE), affects neural development, preference and exploratory behavior, and neural networks associated with spatial memory. In this study, we examined the influence of EE on neural activation in the hippocampal formation (HF) primary excitatory pathway. The last trial of an object in place (OiP) task, in which rats interacted with newly placed but familiar objects in an open field, was used to stimulate hippocampal activity. A group of non-enriched Long Evans rats (*n*=14), housed in shoebox cages, completed a 3-trial OiP task and then 60 min in quiet/dark prior to being sacrificed. Enriched rats (*n*=16), housed similarly, experienced the same task after 18, 90-min EE sessions between postnatal days 25 and 48. Examining neural activation after Trial 3 of the 3-trial OPP task showed how exposure to an environment with consistently and newly placed familiar objects evoked activity within major input and output regions of the HF, including CA1, CA2, CA3, dentate gyrus (DG), and subiculum. Brain tissue was processed using immunohistochemistry to visualize c-FOS protein expression, a marker of neural activation, and neural densities were quantified via microscopy

and stereology. FOS+ cell densities of EE and control rats were normalized using counts from brains without EE or task exposure. Then, evoked activity data from EE and control brains was compared. For the HF as a whole, a history of EE reduced neural activation ($p < 0.05$). In primary input and output areas, DG (-136%, $p < 0.06$) and CA1 (-215%, $p<.02$), respectively, EE history reduced evoked neural activity; however, internal processing areas CA2 (-77%) and CA3 (-118%) did not show statistically significant activity change from controls. In subiculum, a primary output zone, EE reduced evoked neural activity relative to controls (-1,175%, $p < 0.01$). The results suggest that an enrichment history suppresses neural activation evoked by OiP task performance as signal moves sequentially throughout the HF. Because EE rats were exposed routinely to novel placement of familiar objects, which occurred at random during enrichment sessions, habituation to such experience may be responsible for the observed forward moving reduction in neural activity in the HF as well as the rather profound decreased neural activation in the HF output zone.

Disclosures: M. Pavelka: None. **R. Salinas:** None. **M.C. Zrull:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.17/D42

Topic: A.09. Adolescent Development

Title: Testosterone enhances survival of pubertally born cells in the mouse posterodorsal medial amygdala

Authors: *J. L. KIM[1], S. M. BREEDLOVE[2], C. L. JORDAN[2], C. L. SISK[3]
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Abstract: During puberty, the brain undergoes extensive structural remodeling, including the addition of new neurons and glia. Our lab previously found that pubertal cytogenesis occurs in the mouse brain, with a sex difference in the number of pubertally born cells favoring males in the adult posterodorsal medial amygdala (MePD). The MePD is sexually dimorphic with the male MePD being larger in volume than in females, and containing more and larger cells. Studies in rats found that this sexual dimorphism is maintained by adult testosterone. However, whether testosterone influences cell number by affecting the proliferation and/or survival of pubertally born cells is unknown. In this study, we examined the effects of pubertal and adult testosterone on the number of pubertally born cells in the MePD of adult male mice. On P26, male mice were castrated and received a blank or testosterone-filled capsule. During puberty (P28-P49), all mice were given daily injections of cell birth date marker bromodeoxyuridine (BrdU; 200 mg/kg; ip). On P60, all capsules were removed and half the mice of each pubertal

treatment group received a blank capsule, while the other half received a testosterone-filled capsule. All mice were perfused on P90. The brains were sectioned and stained for BrdU-immunoreactive (ir) cells. An ANOVA revealed significant group differences on the total number of BrdU-ir cells in the MePD ($F(3,33)=13.1$, $p=.00$). Post hoc analyses showed that males that received testosterone during both puberty and adulthood had significantly more pubertally born MePD cells ($M=654.78$, $SE=46.51$) than all other groups ($ps<0.05$). In addition, males that received testosterone during puberty, but not adulthood ($M=493.4$, $SE=32.7$), had more BrdU-ir cells in the MePD than males that did not receive testosterone during puberty or adulthood ($M=329.7$, $SE=41.8$) ($p=0.03$). Similarly, males that received testosterone during adulthood, but not puberty ($M=456.1$, $SE=24.5$), had a larger number of BrdU-ir cells compared with males that received no testosterone during either puberty or adulthood (non-significant trend, p=0.10). Overall, it appears the presence of testosterone during puberty and adulthood may have an additive effect, maximizing the number of pubertally born cells found in the adult male MePD. Because testosterone treatment nearly 2 weeks after the end of BrdU treatment increased the adult number of pubertally born cells in the MePD, testosterone likely regulates their adult number by promoting survival, possibly mediating the emergence of sociosexual behaviors. Future studies will aim to address the functional significance of these pubertally born cells on adult male behaviors.

Disclosures: J.L. Kim: None. **S.M. Breedlove:** None. **C.L. Jordan:** None. **C.L. Sisk:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.18/D43

Topic: A.09. Adolescent Development

Title: Social shuffling during adolescence and its impact on pubertal cytogenesis and resulting behavior in adulthood

Authors: *K. T. WILKS[1], J. L. KIM[2], C. L. SISK[3]
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Abstract: Previous studies have shown that mice thrive from social interactions and experience significant negative impact when socially isolated. Social isolation during adolescence negatively affects neurogenesis in the dentate gyrus of the hippocampus and promotes increased anxiety and depression- like behaviors in mice. Social instability, i.e., frequent changes in social partners, has not been given much attention despite social interaction being a key component in development of mice. As a social environment does not naturally consist of only familiar individuals, it is important to look at how a shift in social partners affects the developing brain. This study aimed to examine how an unstable social environment during puberty, i.e., a

constantly changing cage-mate, affects pubertal cytogenesis as well as anxiety and depression-like behaviors in adulthood. Female mice were pair-housed with an age-matched cage-mate during puberty (postnatal day (P) 28-56), with one group housed with a constant cage-mate throughout puberty and another group introduced to a novel cage-mate twice a week. Both groups received the cell birth-date marker bromodeoxyuridine (BrdU) [1mg/ml in drinking water] for one week during early puberty (P28-34). In adulthood (P62-P64), all subjects underwent the open field test and sucrose preference test. All animals were sacrificed on P64. The brains were sectioned and stained for BrdU-immunoreactive (ir) cells. Quantitative analysis revealed no significant difference between groups in the density of BrdU-ir cells in the dentate gyrus (t = -0.03, p = 0.97). In addition, there were no significant differences between groups in depression-like behaviors as measured by the sucrose preference test (t = 0.48, p = 0.64), or in anxiety-like behaviors as measured by the open field test. However, there were large effect sizes present for some open-field behaviors; specifically, the shuffled cage-mate group tended to exhibit greater movement time (t = 2.07, p = 0.06, d = 1.04), greater horizontal activity (t = 2.11, p = 0.05, d = 1.05), greater total distance traveled (t = 1.40, p = 0.18, d = 0.70), and lower rest time (t = -2.01, p = 0.05, d = 1.04) than the stable cage-mate control group. These exploratory behaviors are typically associated with less anxious mice, though. The overall absence of differences between stable and shuffled cage-mate groups suggests that female mice do not find social instability stressful. Females are typically less territorial than males, and may be better equipped to handle unfamiliar social partners.

Disclosures: **K.T. Wilks:** None. **J.L. Kim:** None. **C.L. Sisk:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.19/D44

Topic: A.09. Adolescent Development

Support: Washington College Psychology Department

Title: Effects of weaning time-point and sex on separation anxiety during development

Authors: *C. R. FIGIEL, C. J. GIBSON
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Abstract: Weaning may be stressful and induce separation anxiety. Behavioral and physiological changes have been documented in early vs. typical weaning. This study examined typical vs. late weaning. Pups were tested for anxiety either immediately or 5 weeks after weaning. Results indicated less anxiety in females, late weaning, and late testing conditions on the raised plus-maze. There was more myelination deposition in females than males. No

significant differences were found for corticosterone serum levels in an ELISA assay or for myelin basic protein (MBP) expression.

Disclosures: C.R. Figiel: None. **C.J. Gibson:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

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Program#/Poster#: 121.20/D45

Topic: A.09. Adolescent Development

Support: R01MH098003

R01NS085200

Title: Tracing the developmental trajectories of neural circuit using resting-state functional connectivity in awake rats

Authors: *Z. MA[1], Y. MA[1], N. ZHANG[1,2]
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Abstract: Childhood and adolescence are both phases characterized by rapid social, emotional, and cognitive growth. During these transition periods, the brain undergoes a complex and dynamic maturational process that contains multiple stages. These stages are marked by notable neuronal changes such as myelination of axons, synaptic pruning. In addition, cell morphology, neural transmitter and receptor density also change drastically during early brain development. Protracted development during childhood and adolescence makes the brain particularly vulnerable to adverse early-life experience. In fact, neuropsychiatric disorders often emerge during childhood and persist across the lifespan. Therefore, understanding postnatal brain development is crucial for uncovering brain function in health and disease. However, most of recent rodent studies have only focused on the neurobiological as well as behavioral aspect on brain development. Lack of these knowledge has highlighted a critical gap in establishing a full understanding of animal models of development-related brain disorders. To comprehensively trace the developmental trajectories of individual neural circuits and functional organization of large-scale brain network, here we longitudinally acquired rsfMRI data in awake rats during five developmental stages: juvenile (P30-P31), early adolescence (P34-P35), adolescence (P41-P42), late adolescence (P48-P49) and adulthood (P70-P90). We discovered that the functional development of brain circuits has system specific trajectories, and exhibits hemispheric lateralization. In addition, we discovered that among these changes, different brain regions exhibited distinct developmental trajectories that are age specific. Furthermore, we showed that

whole-brain network development is characterized by reduced segregation (i.e. local communication) but increased integration (FC between distant regions).

Disclosures: **Z. Ma:** None. **Y. Ma:** None. **N. Zhang:** None.

Poster

121. Animal Models: Impact of Environment on the Brain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 121.21/D46

Topic: A.09. Adolescent Development

Support: AA019767

AA11605

AA007573

AA021040

Title: Voluntary exercise restores adolescent binge ethanol-induced loss of basal forebrain cholinergic neurons in adulthood

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Abstract: Binge drinking and alcohol abuse are common during adolescence. Using the preclinical adolescent intermittent ethanol (AIE; 5.0 g/kg, i.g., 2-day on/2-day off from postnatal day [P]25 to P55) model of human adolescent binge drinking, we find reductions of basal forebrain cholinergic neuron populations that persist from late adolescence (P55) into adulthood (P220), an effect that we replicated in the post-mortem human alcoholic basal forebrain. Basal forebrain cholinergic neuron loss might lead to long-term changes in adult neurobiology. We tested the hypothesis that voluntary exercise would restore the AIE-induced loss of basal forebrain cholinergic neurons. In Experiment 1, wheel running from P24 to P80 prevented the AIE-induced loss of choline acetyltransferase (ChAT) immunoreactive neurons as well as additional cholinergic markers (i.e., $p75^{NTR}$ and TrkA) in the adult basal forebrain. In Experiment 2, wheel running from P56 (24 hr after the conclusion of AIE) to P95 reversed the AIE-induced loss of cholinergic neuron markers in the adult (P95) basal forebrain. Exercise also reversed the AIE-induced behavioral flexibility impairments on the Morris water maze in adulthood. While the mechanism underlying the AIE-induced loss of cholinergic phenotype remains to be fully elucidated, the data implicate induction of the innate immune system. Wheel running blunted AIE-induced upregulation of several innate immune signaling genes.

Administration of the anti-inflammatory drug indomethacin during AIE prevented the loss of ChAT-, $p75^{NTR}$-, and TrkA-immunoreactive neurons. Treatment with the endotoxin lipopolysaccharide mimicked, but did not potentiate, the AIE-induced loss of cholinergic marker expression. Diminished neurotrophic support may constitute an additional mechanism underlying the AIE-induced loss of cholinergic neurons. Expression of TrkA and $p75^{NTR}$, which are both receptors for the neurotrophin nerve growth factor (NGF), are diminished by AIE. Basal forebrain-to-hippocampal NGF inputs are critical for the survival of cholinergic neurons, and AIE reduced gene expression of NGF and other neurotrophins in the adult hippocampus, consistent with disruption of basal forebrain neurotrophic support. Together, these data reveal that voluntary exercise in the form of wheel running restores the AIE-induced loss of basal forebrain cholinergic neurons, an effect that may involve a shift in the innate immune-neurotrophic balance. Further, these data reveal that AIE does not cause cholinergic neuron degeneration highlighting the potential for the development of therapeutics. Supported by the NADIA of the NIAAA.

Disclosures: R.P. Vetreno: None. **F.T. Crews:** None.

Poster

122. HCN, TRP, and Other Ion Channels

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Program#/Poster#: 122.01/D47

Topic: B.04. Ion Channels

Support: Heart and Stroke Foundation of Canada G-14-0006260

Title: The elusive channel driving ischemic spreading depolarization

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Abstract: Neurons of the higher brain immediately undergo spreading depolarization (SD) in response to ischemia resulting from heart failure, traumatic brain injury or focal stroke. At SD onset, neurons cease firing, swell and can die within minutes. A study of pyramidal neurons using whole-cell voltage clamp by Czeh et al. (1993) showed that the macro-conductance driving SD is inward, cationic, non-selective and reverses near zero millivolts. Like ischemic SD itself, this conductance resists blockers of standard voltage- and ligand-gated channels. Na channel blockers merely delay SD onset. We used neocortical slices from adult rat to record channel activity in patches under voltage clamp during oxygen-glucose deprivation (OGD) at 35ºC. Using the cell-attached configuration (CAC), patches were recorded during bath superfusion with blockers of Na, K, Ca, pannexin and glutamate-related channels. The blockers were also included in the recording pipette solution. This silenced all spontaneous channel activity within 2

minutes of commencing a recording. Nonetheless within 6 to 8 min of OGD, novel channel opening commenced. The mean unitary current (+/- st. dev.) was 1.7 +/- 0.17 pA at holding potential (h) = -70 mV (n=5 patches). Unitary event frequency increased, as did multiple channel openings, until the patch was lost during full-onset SD. More positive h values reversed the unitary current near 0 mV, implicating a Na/K conductance. In support, the channel properties appeared unaltered by substituting K for Na in the patch pipette. Under CAC, the neuronal membrane potential is not accessible but can be estimated. The slope conductance was ~28 pS based on unitary pA values from 23 neurons spanning h= -90 to +50 mV. The marine poison palytoxin (PLTX) is well characterized as specifically binding externally to the Na/K pump, converting it into an open Na/K channel. Bath PLTX also induces SD in neocortical slices (10 to 100 nM). Cell-attached patch recording with 1 pM PLTX in the pipette (again, blockers in the pipette and extracellularly) opened a unitary channel of 1.7 +/- 0.3 pA (n=7; h= -70 mV), similar to the OGD-evoked channel described above. In outside-out patches, 1 pM PLTX + blockers in the bath also opened this channel (1.9 +/- 0.05 pA; n=4; h= -70 mV). We are currently testing if this channel displays any mechanosensitivity although TRPM7 inhibition does not block or delay SD. We propose that OGD induces conversion of the Na/K pump into an open Na/K channel that then drives spreading depolarization.

Disclosures: P.J. Gagolewicz: None. **R.D. Andrew:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

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Program#/Poster#: 122.02/D48

Topic: B.04. Ion Channels

Support: NIH Grant U01 MH105941

ADA Grant 1-17-ACE-31

Einstein-Mt. Sinai Diabetes Research Center Pilot and Feasibility Award

Alexander and Alexandrine Sinsheimer Scholar Award

Title: Optimizing a TrpV1 system for the remote regulation of cells

Authors: *J. NAM[1], S. A. STANLEY[2]
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Abstract: The central nervous system plays a substantial role in metabolic disorders such as diabetes. Remote regulation is an invaluable method for elucidating the pathways involved, but

in studying a system as sensitive as glucose metabolism, difficulties arise with more invasive methods like optogenetics and chemogenetics. A method of remote regulation, involving iron oxide nanoparticles bound to the transient receptor potential vanilloid 1 receptor (TrpV1), and subsequent activation of the channel by treatment with radio waves or magnetic fields, has been demonstrated to regulate blood glucose levels both *in vitro* and in murine studies *in vivo*. Additionally, this ion channel has been found to be activated by multiple modalities including temperature, mechanical force, and voltage. Thus we optimized the TrpV1 channel, by generating mutants with altered sensitivity to these modalities, to reduce background signaling and improve the temporal resolution and sensitivity of channel activation for use in magnetogenetics. We tested the activity of the receptor using GFP-ferritin constructs within HEK-293T cells, by subjecting them to external factors including temperature, agonists, and magnetic field treatment. We then assayed the activity with methods such as luciferase reporter systems and calcium imaging. These TrpV1 channel variants may provide us with better tools for the remote regulation of cells.

Disclosures: J. Nam: None. **S.A. Stanley:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.03/D49

Topic: B.04. Ion Channels

Support: NSF EAGER 1535790

Title: *Drosophila*-inspired molecular thermosensors

Authors: *B. R. BERIGAN[1], M. AMIRSHENAVA[1], A. SALARI[2], A. MISHRA[1], K. MIGUEL[3], B. C. ZARS[1], J. L. LIN[1], T. ZARS[1], M. MILESCU[1], L. S. MILESCU[1]
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Abstract: Gustatory receptors are a family of transmembrane proteins that have been extensively studied in the context of insect taste and odor sensory system. A recent study has identified a *Drosophila melanogaster* gustatory receptor, Gr28b(D), as a thermosensor expressed in peripheral “hot cell” neurons responsible for rapid heat avoidance. Gr28b(D) is the first gustatory receptor shown to be involved in thermosensation. However, virtually nothing is known about the structure of the protein, and fundamental questions about its biophysical properties remain completely unanswered. We were able to heterologously express Gr28b(D) in *Xenopus laevis* oocytes and confirm temperature-sensitivity as a potentially intrinsic property of the protein. Furthermore, we tested Grs from other *Drosophila* species and find that they exhibit distinct

temperature responses. We have generated chimaeras between these various Grs to investigate structural correlates of ion selectivity and temperature sensitivity. Additionally, we co-expressed Grs and calcium sensors (GCaMP6s or GCaMP6f) in *D. melanogaster* motor neurons to test for correlation between neuronal firing frequency and temperature. We used an integrated platform for real-time 3D mapping of neural circuits in behaving animals and electrophysiology (milesculabs.biology.missouri.edu) to measure changes in neuronal activity, via fluorescence imaging. These results are valuable for guiding future work on designing thermogenetic tools that can be used in isolation or in combination with optogenetics to control cellular and network excitability.

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Poster

122. HCN, TRP, and Other Ion Channels

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Topic: B.04. Ion Channels

Support: JSPS KAKENHI Grant 15K19197

JSPS KAKENHI Grant 15H02501

Kato Memorial Bioscience Foundation

Title: Pharmacological effects of 4-isopropylcyclohexanol on TRP channel and ANO1/TMEM16A

Authors: *Y. TAKAYAMA[1], H. FURUE[2], M. TOMINAGA[3]
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Abstract: Transient receptor potential (TRP) channels and anoctamin 1 (ANO1) interactions have a lot of physiological significance in our body. For instance, TRPV4-ANO1 interaction could be involved in secretion of cerebrospinal fluid from choroid plexus epithelial cells, and TRPV1-ANO1 interaction enhances nociceptive signals in primary sensory neurons. Through the investigation to search other TRP-ANO1 interactions, we found that a TRPM8 agonist, menthol, strongly inhibits ANO1 currents activated by high concentrations of intracellular free calcium. Moreover, isopropylcyclohexane was identified as a core chemical structure to inhibit ANO1 currents. This finding indicated that isopropylcyclohexane is one key chemical which could reduce TRPV1-ANO1-mediated pain sensation. However, the action of ANO1 current inhibition

by isopropylcyclohexane (within 3 min) was slower than that of menthol (within 30 sec). To overcome the problem, we focused on hydrophilicity of the chemical and found that a more hydrophilic compound, 4-isopropylcyclohexanol, rapidly inhibits ANO1 currents similar to menthol. Therefore, we investigated the analgesic effects of 4-isopropylcyclohexanol in mice. 4-isopropylcyclohexanol, a kind of flavor- or food-additive, also inhibited capsaicin (100 nM)-induced TRPV1 currents. Interestingly, the inhibitory mechanism was not channel pore blocking, but the chemical reduced only open time of single channels. In addition, 4-isopropylcyclohexanol strongly inhibited capsaicin-induced depolarization and action potential generation in small dorsal root ganglia (DRG) neurons of mice. Furthermore, 4-isopropylcyclohexanol inhibited ANO1 currents but also currents mediated by TRPV1, TRPA1 or TRPV4. 4-isopropylcyclohexanol reduced capsaicin-evoked pain-related behaviors in mice while 4-isopropylcyclohexanol alone did not. These results suggest that multiple inhibitory effects by one chemical are also important to reduce acute pain sensation. Thus, 4-isopropylcyclohexanol could be an important chemical compound to develop novel analgesic or antipruritic agents.

Disclosures: **Y. Takayama:** None. **H. Furue:** None. **M. Tominaga:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.05/D51

Topic: B.04. Ion Channels

Support: DAAD-Research Grant, Doctoral programmes in Germany

Title: TRPM4 in CA1 hippocampal physiology

Authors: *B. FEAREY[1], D. MENSCHING[2], L. BINKLE[2], T. G. OERTNER[1], M. A. FRIESE[2], C. E. GEE[1]
[1]Inst. for Synaptic Physiol., Ctr. For Mol. Neurobio., Hamburg, Germany; [2]Inst. for Neuroimmunology and Multiple Sclerosis, Ctr. for Mol. Neurobio., Hamburg, Germany

Abstract: The transient receptor potential melastatin four (TRPM4) is a calcium-activated monovalent cation channel that has been found in both excitable and non-excitable cells. In a mouse model of multiple sclerosis, a lack of the TRPM4 channel results in a reduced clinical disease score and ameliorated neurodegeneration. Additionally, absence of TRPM4 *in vitro* protects against neuronal excitotoxicity. Few studies have explored the function of TRPM4 in the hippocampus and its possible participation in synaptic plasticity. We hypothesized that TRPM4 may be activated by calcium entry and release during synaptic stimulation and may boost excitatory transmission. As a first step, we wanted to characterize the expression of TRPM4

protein in the hippocampus, which is unknown. We tested several commercially available anti-TRPM4 antibodies in hippocampal brain slices, but could not detect convincing staining in wildtype versus TRPM4 KO mice. Consequently, we used CRISPR/Cas9 to add a GFP tag to the endogenous TRPM4. Using this mouse line, we are currently characterizing the expression of the channel in the brain and how excitotoxicity might change the expression pattern. Secondly, using calcium indicators and two-photon microscopy, we characterized whether TRPM4 contributes to spine calcium signals during excitatory synaptic transmission in CA1 pyramidal neurons. Synaptically-evoked spine calcium signals were unaffected by wash-in of TRPM4 antagonists. Evoked EPSPs in hippocampal CA1 pyramidal neurons from wild type mice also showed no change in the presence of the TRPM4 antagonists, 9-phenanthrol or glibenclamide. This suggests that TRPM4 does not contribute to unitary EPSPs or spine calcium signals in CA1 pyramidal neurons. It is possible however, that a significant contribution of TRPM4 in the physiology of the cell is only apparent following neuronal injury, or that other cell types in the hippocampus more strongly express TRPM4 and promote excitotoxicity. These possibilities will be explored in upcoming experiments.

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Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

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Program#/Poster#: 122.06/D52

Topic: B.04. Ion Channels

Title: Characterization of HC-070: A potent and selective antagonist of TRPC4 and TRPC5 containing channels

Authors: *J. A. CHONG[1], T. T. STRASSMAIER[1], R. J. GALLASCHUN[1], S. JUST[2], C. EICKMEIER[2], A. SAUER[2], N. T. BLAIR[1], C. FANGER[1], J. WITEK[1], D. DEL CAMINO[1], M. M. MORAN[1], B. L. CHENARD[1]
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Abstract: TRPC4 and TRPC5 channels are calcium-permeable, non-selective cation channels expressed at high levels in the central nervous system. Genetic deletion of these channels results in an anxiolytic phenotype and reduced CCK signaling in the amygdala. Chemical probes are powerful research tools that can spur the development of new medicines but are only useful if they are potent, specific, and selective. We therefore sought to develop high-quality probe compounds suitable for in vivo experimentation to further elucidate the role of TRPC4 and TRPC5 containing ion channels. To this end, we performed a hight-throughput screen to identify

TRPC5 antagonists. We confirmed the most promising of these compounds using the whole-cell patch clamp. Through additional cycles of medicinal chemistry optimization we invented HC-070 which has the properties to serve as a useful in vitro and in vivo probe.
HC-070 inhibits TRPC4 and TRPC5 homomultimers as well as TRPC1/5 and TRPC1/4 heteromultimeric channels with nanomolar potencies. The compound is highly selective and specific, showing more than a 1,000-fold preference for TRPC4 and TRPC5 over more than 100 other targets assessed as well as TRPC6. The in vitro potency and selectivity of this compound are very similar to a compound we previously invented and disclosed, HC-608, which has also been referred to as Pico145.
When administered to brain slices, HC-070 attenuates CCK-4 mediated post synaptic currents in the basolateral amygdala, consistent with previously reported experiments relying on TRPC4 and TRPC5 knockout animals. This observation suggests that HC-070 blocks native as well as heterologously expressed channels.
The presence of plasma only reduces the apparent potency of HC-070 approximately 10-fold thereby indicating potential utility in vivo.
In summary, we invented a highly potent and selective inhibitor of TRPC4 and TRPC5 containing channels that fulfills the general criteria for a high-quality chemical probe. This compound exerts effects in both heterologous expression systems and brain slices. Additional work, described in our companion poster, highlights the utility of this compound as a useful tool for behavioral work as well. We expect HC-070 to be important in the further elucidation of the role of TRPC4 and TRPC5 channels both in vitro and in vivo.

Disclosures: **J.A. Chong:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **T.T. Strassmaier:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **R.J. Gallaschun:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **S. Just:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **C. Eickmeier:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **A. Sauer:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **N.T. Blair:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **C. Fanger:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **J. Witek:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **D. Del Camino:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **M.M. Moran:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **B.L. Chenard:** A. Employment/Salary (full or part-time):; Hydra Biosciences.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.07/D53

Topic: B.04. Ion Channels

Title: Pharmacological inhibition of TRPC4 and TRPC5 with HC-070 in rodents mimics the effects on behavior associated with anxiety and depression previously seen with corresponding gene deletion models

Authors: S. JUST[1], A. CECI[1], A. SAUER[1], C. EICKMEIER[1], K. BAUM-KROKER[1], S. CANTIN[2], M. D'AMOURS[2], R. J. GALLASCHUN[2], B. HENGERER[1], S. MALEKIANI[2], H.-J. MARTIN[1], R. MIHALEK[2], J. MCLAUGHLIN[2], H. SCHAUERTE[3], E. SEIFRITZ[3], H. SIGIRST[3], C. R. PRYCE[3], B. CHENARD[2], *M. M. MORAN[2]
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Abstract: Genetic deletion of TRPC4 and TRPC5 results in an anxiolytic phenotype. We sought to determine if the behavioral effects observed in such knockout mice could be recapitulated by acute pharmacological inhibition using a potent and selective TRPC4/5 antagonist that we recently invented, HC-070 (see companion poster for in vitro characterization).
In mouse and rat pharmacokinetic studies, HC-070 was found to have a low clearance and a moderate volume of distribution. When orally administered in a methylcellulose suspension, HC-070 achieved exposures in the brain and plasma that were deemed sufficient to test behavioral activity.
Since effects on CCK-signaling in the amygdala were observed with both TRPC4 and TRPC5 knockouts, we tested the ability of HC-070 to impact the effects of CCK-4 in the elevated plus maze (EPM). Consistent with in vitro results, we found that HC-070 (1 mg/kg PO) increases entries into the open arm of an EPM after CCK-4 exposure. The compound is as efficacious as diazepam, a reference anxiolytic, in a standard EPM maze model (no CCK) and reduces marble-burying in a test of obsessive-compulsive behaviors. These data suggest that blocking TRPC4/5 channels can relieve ethological anxiety behaviors.
In the forced swim test (FST), a model thought to reflect learned helplessness, HC-070 (1 mg/kg PO) reduces the time mice spend immobile. A careful study of the pharmacokinetic-pharmacodynamic relationship demonstrates that the half-maximal effect in the FST coincides with the unbound compound levels corresponding to the IC50s forTRPC4 and TRPC5 inhibition, thereby increasing confidence that the observed effects are on target. Additionally, oral treatment with HC-070 did not induce hyperactivity in normally behaving animals.
In a model of chronic social defeat, in which mice endured daily attacks by aggressive dominant mice, oral administration of HC-070 reduces freezing responses to a conditioned stimulus. This effect only manifests in mice that are exposed to the stressor – control mice treated with HC-070 acquire the fear-induced freezing behavior normally.
The behavioral effects observed with HC-070 may be partially due to reduced glutamate transmission as the elevation in glutamate levels induced by restraint stress is attenuated in HC-070 treated rats compared to vehicle-treated animals.
Taken as an ensemble, these results suggest that TRPC4 and TRPC5 containing channels may represent important therapeutic targets for the development of new psychiatric medicines. Further studies with HC-070, which shows robust *in vivo* activity, will help further illuminate the role of these fascinating channels.

Disclosures: **S. Just:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **A. Ceci:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **A. Sauer:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **C. Eickmeier:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **K. Baum-Kroker:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **S. Cantin:** None. **M. D'Amours:** A. Employment/Salary (full or part-time):; Hydra Biosciences. **R.J. Gallaschun:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **B. Hengerer:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **S. Malekiani:** A. Employment/Salary (full or part-time):; Hydra Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **H. Martin:** A. Employment/Salary (full or part-time):; Boehringer-Ingelheim. **R. Mihalek:** None. **J. McLaughlin:** None. **H. Schauerte:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boehringer-Ingelheim. **E. Seifritz:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boehringer-Ingelheim. **H. Sigirst:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boehringer-Ingelheim. **C.R. Pryce:** 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.; Boehringer-Ingelheim. **B. Chenard:** A. Employment/Salary (full or part-time):; Hydra Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences. **M.M. Moran:** A. Employment/Salary (full or part-time):; Hydra Biosciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Hydra Biosciences.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.08/D54

Topic: B.04. Ion Channels

Title: Activity-dependent regulation of tonic firing by type 1 metabotropic glutamate receptors via TRPC3 in substantia nigra dopamine neurons

Authors: *K. UM[1], L. BIRNBAUMER[2], H. KIM[1], M. PARK[1]
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Abstract: Pacemaker dopamine neurons in the substantia nigra pars compacta (SNc) exhibit low-frequency tonic firing without any input stimuli and often produce high-frequency burst firing in response to strong glutamatergic afferent inputs. Since the tonic firing determines ambient dopamine levels, regulation of tonic firing rate is very important. In SNc dopamine neurons, activation of type 1 metabotropic glutamate receptors (mGluR1) appears to enhance tonic firing rates. Although activation of mGluR1 is reported to increase cell excitability via activation of some type of TRP channels, it is still unclear how mGluR1 regulates tonic firing activities in SNc dopamine neurons. In this study, we present that mGluR1 regulates tonic firing rate activity-dependently via TRPC3 channels in SNc dopamine neurons. In SNc dopamine neurons, activation of mGluR1 inhibited spontaneous firing transiently but subsequently led to a slow increase in the tonic firing rate. DHPG, a mGluR1 agonist, evoked two clear phases of Ca^{2+} elevations: the fast Ca^{2+} surge released from the endoplasmic reticulum Ca^{2+} store and then the following sustained Ca^{2+} influxes. While the initial Ca2+ surge inhibited spontaneous firing, the sustained Ca^{2+} influxes occurred together with the tonic firing enhancement, indicating the involvement of continuous activation of depolarizing currents and sustained firing-induced Ca2+ influxes. These mGluR1-induced Ca^{2+} influxes were dramatically reduced by pre-treatment of TRPC3 channel blockers. Moreover, when we depleted Ca^{2+} stores by thapsigargin, the mGluR1-induced sustained Ca^{2+} influxes still survived. In addition, stimulations of mGluR1 by DHPG or repetitive mGluR1-mediated electrical synaptic stimuli increased tonic firing rates in wild-type SNc dopamine neurons, but they failed in TRPC3 knock-out mice. From these results, we could conclude that of mGluR1 slowly enhance tonic firing rate via activation of TRPC3 channels in an activity-dependent way in SNc dopamine neurons.

Disclosures: K. Um: None. **L. Birnbaumer:** None. **H. Kim:** None. **M. Park:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.09/D55

Topic: B.04. Ion Channels

Title: Chemical Neuro Stimulation of TRPV1 and TRPA1 by FLX-787 elicits synergistic signaling to promote human efficacy in conditions with high-prevalence muscle cramping

Authors: *G. SHORT, B. HEGARTY, J. SZEGDA, D. CABRAL-LILLY, J. CERMAK, C. WESTPHAL, T. WESSEL
Flex Pharma Inc, Boston, MA

Abstract: Chemical Neuro Stimulation describes a method to treat neurological disorders by stimulating sensory neurons with small molecules to alter the behavior of distinct neural circuits within the central nervous system. FLX-787, a co-activator of TRPV1 and TRPA1, stimulates

sensory fibers in the mucosa of the oropharynx and esophagus and is thought to activate serotonergic and noradrenergic brainstem nuclei that modulate α-motor neuron circuitry via descending pathways in the spinal cord. To understand the early events initiating this mechanism, we measured Ca^{2+} influx after TRPA1 and TRPV1 co-activation in human DRG neurons *ex vivo* and neural responses from recordings in the rat chorda tympani. We found that ~25% of the DRG population responded to a combination of both TRPV1 (50 nM capsaicin) and TRPA1 (100 μM cinnamaldehyde) activation evoking a supra-additive response. FLX-787 was observed to promote a similar response in DRGs increasing Ca^{2+} influx, as well as prolonging a state of non-desensitizing activation lasting between 5-10 minutes. Supra-additive responses were also observed in rat chorda tympani when co-stimulated with both TRPV1 (1 μM capsaicin) and TRPA1 (0.01% mustard oil) activators. While both agents provided robust chorda tympani responses individually, co-application of the TRP activators elicited a synergistic increase in chorda tympani signaling mirroring our findings in DRGs.
These data suggest that in a subset of human sensory neurons expressing both ion channels, co-activation of TRPV1 and TRPA1 may promote a synergistic neural response that is different from the response mediated by either ion channel alone. Given that FLX-787 significantly reduces muscle cramping in clinical studies [electrically-induced cramps ($p < 0.001$) and nocturnal leg cramps ($p=0.03$)] but individual activators of TRPV1 or TRPA1 do not, efficacy in man may be linked to TRPV1 and TRPA1 synergistic signaling and subsequent reduction of α-motor neuron hyperexcitability. Phase 2 clinical studies using FLX-787 are underway in the United States and Australia in indications with a high-prevalence of muscle cramps and spasms including MS, ALS and Charcot-Marie-Tooth disease.

Disclosures: **G. Short:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **B. Hegarty:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **J. Szegda:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **D. Cabral-Lilly:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **J. Cermak:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **C. Westphal:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma. **T. Wessel:** A. Employment/Salary (full or part-time):; Flex Pharma. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.10/D56

Topic: B.04. Ion Channels

Title: Characterization of background Na^+ channel important for pacemaking in Substantia nigra dopamine neurons

Authors: *S. HAHN, S. KIM, H. KIM, M. PARK
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Abstract: Dopamine neurons in the midbrain are slow pacemakers that generate regularly spontaneous firing. Since resting membrane potentials of dopamine neurons are maintained between -55-45 mV far from the equilibrium potential of K^+(E_k), there could be a conductance responsible for persistent depolarization of membrane potential. NALCN channel appears to be a good candidate for Na^+ leak currents and, if so, they could also regulate pacemaker activity in dopamine neurons. Therefore, we have investigated background Na^+ -permeable ion channel responsible for maintaining membrane potential depolarized in nigral dopamine neurons. Since Ca^{2+}-sensing receptors and many neuropeptides regulate NALCN activities, we examined whether extracellular Ca^{2+} and Na^+ influence membrane potentials, firing rates, and inward currents in dopamine neurons. Lowering $[Ca^{2+}]_e$ from 2.0 to 0.5mM increased the Na^+ leak inward current and heavily affected spontaneous firing rates. A nonselective cation channel blocker for TRPC channels, SKF96365, did not completely block background Na^+ conductances. Despite the usage of TTX and Cs^+ which block Na_v and K_v channels, the component of Na^+ leak conductances survived. In addition, neurotensin(NT) and substance P(SP) increased the Na^+ inward current and tonic firing rates. These results suggest that NALCN could play an important role in the generation and regulation of pacemaker activities of the nigral dopamine neurons.

Disclosures: S. Hahn: None. **S. Kim:** None. **H. Kim:** None. **M. Park:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

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Topic: B.04. Ion Channels

Support: NIHMH086828

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Title: The essential roles of GluA1 phosphorylation and presynaptic HCN channels in fast-acting antidepressant responses of ketamine

Authors: *X. CAI[1], K. ZHANG[1], T. XU[1], Z. WEI[2], V. N. YAMAKI[1], R. L. HUGANIR[3], M. HUANG[2]
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Abstract: The mechanism underlying the rapid antidepressant actions of ketamine is still obscure. Here we show that ketamine potentiated Schaffer collateral-CA1 cell excitatory synaptic transmission and enhanced GluR1 S845 phosphorylation at hippocampal area CA1. These effects were not occluded by GABA receptor blockade. Ketamine reduced anhedonia and behavioral despair in wild type mice subjected to chronic mild stress, but had no effect in GluR1 S845A knock-in mutant mice. The enhancement of excitatory synaptic transmission and antidepressant actions of ketamine required presynaptic but not postsynaptic NMDA receptors and were occluded by HCN channel inhibition or deletion. Our results implicate that presynaptic NMDA receptor inhibition is required for the fast-acting antidepressant responses of ketamine, which could cause downregulation of the presynaptic HCN channels and promotion of glutamate release, thus enhancing the postsynaptic AMPA receptor phosphorylation and exocytosis

Disclosures: X. Cai: None. **K. Zhang:** None. **T. Xu:** None. **Z. Wei:** None. **V.N. Yamaki:** None. **R.L. Huganir:** None. **M. Huang:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.12/D58

Topic: B.04. Ion Channels

Title: ANO9 is a cation channel activated by the cAMP/PKA pathway

Authors: *H. KIM[1,2], U. OH[1]
[1]KIST, Seoul, Korea, Republic of; [2]Pharm., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Anoctamin is transmembrane protein containing 10 family proteins. ANO1 and ANO2 are well known as Calcium-activated chloride channel. ANO6 is calcium permeable scramblase. However, ANO9 and others function are not identified yet. In this research, ANO9 is cation permeable channel activated by intracellular cAMP. ANO9 currents including calcium influx was confirmed by calcium imaging as well as patch clamp. SW480 cells including endogenous hANO9 have also channel activity of intracellular cAMP. And this activity is reduced by ANO9 siRNA.Through ion permeability test, ANO9 shows a permeability of cation, especially to divalent ions. ANO9 opening is mediated by PKA activation. When ANO9 is phosphorylated by PKA, this channel evoke robustly cation current. We confirmed that mutation of phosphorylation site of ANO9 cannot evoke current by cAMP.To summarize, ANO9 phosphorylation site is phosphorylated by cAMP/PKA pathway, ANO9 have channel activity of cation permeable inward current.

Disclosures: H. Kim: None. **U. Oh:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.13/D59

Topic: D.03. Somatosensation: Pain

Title: $Ca_V3.2$ T-type calcium channels are responsible for hyperexcitability of nociceptors in a post-surgical pain model

Authors: *S. JOKSIMOVIC[1], S. M. JOKSIMOVIC[1], V. TESIC[1], A. GARCIA CABALLERO[2], V. JEVTOVIC-TODOROVIC[1], G. W. ZAMPONI[2], S. M. TODOROVIC[1]
[1]Univ. of Colorado, Anschutz Med. Campus, Aurora, CO; [2]Dept. of Physiol. and Pharmacol., Univ. of Calgary, Cumming Sch. of Med., Calgary, AB, Canada

Abstract: Introduction: Several studies show an important role of the $Ca_V3.2$ subtype of T-type calcium channels (T-channels) in chronic pain, however, their role in acute pain resulting from surgical tissue injury is yet to be determined. Therefore, the aim of our study was to investigate whether $Ca_V3.2$ T-channels are involved in development of acute post-operative pain.
Methods: An incisional pain model was developed by performing deep tissue incision of the plantar surface of the hind paw in Sprague-Dawley rats and C57BL/6J mice, wild-type (WT) and $Ca_V3.2$ knock-out (KO). Changes in excitability of DRG cells were measured using current-clamp electrophysiology. The expression level of $Ca_V3.2$ channel in rat DRG cells was determined with qRT-PCR and western blot of DRG tissue 24 and 48 h post-incision. In vivo

assessment of the role of $Ca_V3.2$ channels in post-surgical pain was done by measuring hind paw responses to mechanical stimulus in WT and $Ca_V3.2$ KO mice, as well as after intrathecal application of USP5-shRNA, an important regulator of $Ca_V3.2$ channel ubiquitination.
Results: Current-clamp recordings from dissociated small size DRG cells (<30 μm in diameter) identified three types of neurons by their firing pattern: single, multiple and high-frequency spiking. A noticeable increase of high-frequency spiking neurons was detected 24 and 48 h post-incision, as compared to the sham group ($p=0.041$, Fisher's test). Also, the number of action potentials in sensory neurons after incision was reduced after application of a pan-selective T-channel blocker (TTA-P2), as compared to the baseline [two-way RM ANOVA followed by Sidak's post-hoc; 30, 40 and 50 pA ($p<0.001$)]. In addition, we noticed a significant reduction of action potential frequency in post-incision cells after pre-incubation with 3 μM TTA-P2, as compared to non-incubated cells ($p=0.017$, t-test). Western blots did not reveal any change of $Ca_V3.2$ channel expression post-incision ($p=0.130$, Mann-Whitney test), whereas qRT-PCR showed a slight decrease of $Ca_V3.2$ mRNA (about 20%), as compared to the sham group. However, mechanical sensitivity to punctate stimulus was significantly reduced in mice with selective knock-down of USP5, as well as in global $Ca_V3.2$ KO, when compared to WT mice [two-way RM ANOVA followed by Tukey's post-hoc; 24 h post-incision ($p=0.034$ and $p=0.012$, respectively); 48 h post-incision ($p=0.035$ and $p=0.008$, respectively].
Conclusion: Our study suggests that $Ca_V3.2$ T-channels significantly contribute to the increased excitability of DRG neurons after surgery, most likely due to their enhanced membrane stability, which can be explained by increased activity of deubiquitinating enzyme USP5.

Disclosures: S. Joksimovic: None. **S.M. Joksimovic:** None. **V. Tesic:** None. **A. Garcia Caballero:** None. **V. Jevtovic-Todorovic:** None. **G.W. Zamponi:** None. **S.M. Todorovic:** None.

Poster

122. HCN, TRP, and Other Ion Channels

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.14/D60

Topic: B.04. Ion Channels

Support: NIH AA021657

NIH 022292

Title: The role of TRPV1 channels in the lateral habenula in pain, anxiety and depressive-like behaviors in rats withdrawn from chronic alcohol consumption

Authors: *J. YE[1], D. GREGOR[2], W. ZUO[3], R. FU[4]
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[3]Anesthesiol., Rutgers New Jersey Med. Sch., Newark, NJ; [4]Anesthesiol., Rutgers, The State Univ. of New Jersey, Newark, NJ

Abstract: The Transient Receptor Potential channel, vanilloid type 1 (TRPV1) is a nonselective cation channel. Activation of TRPV1 increases glutamatergic transmission has been shown in several brain regions, and can modulate anxiety and depressive-like behaviors. TRPV1 channels are present in the lateral habenula (LHb), an epithalamic structure that connects the forebrain with the midbrain, processes affective negative signaling and can be activated by noxious stimuli and pain. In the current study, we measured the effect of pharmacological manipulation of TRPV1 in the LHb on pain, anxiety, depressive- and relapse-like behaviors using Hargreaves, elevated plus maze (EPM), forced swim test (FST) and the intermittent access to 2-bottle free choice (IA2BC) paradigm, respectively, in Long-Evans rats at 24 h withdrawal from chronic alcohol drinking in the IA2BC paradigm. Additionally, we recorded electrophysiological events in LHb slices. We found that intra-LHb infusion of the TRPV1 agonist capsaicin (CAPS) increased sensitivity to thermal stimuli in naïve but not in withdrawn rats. Conversely, intra-LHb infusion of TRPV1 antagonist capsazepine (CPZ) reduced sensitivity to thermal stimuli in withdrawn rats, but did not alter pain sensitivity in naïve rats. Also, in withdrawn rats, CPZ reduced the time spent in open arms in the EPM, an effect that was mimicked by CAPS. Conversely, CAPS increased the time spent in open arms in naïve rats. In addition, CPZ increased immobility time in the FST, which was also mimicked by CAPS, in naïve rats. However, neither CPZ nor CAPS had a significant effect on FST in withdrawn rats. Finally, both CPZ and CAPS significantly decreased ethanol consumption. Moreover, both acute ethanol and CAPS enhanced glutamatergic transmission and firing of LHb neurons, but the effect was weaker in withdrawn rats than naïve rats. Over half of the facilitation induced by acute ethanol was attenuated by CPZ, suggesting that hyperactivity of LHb neurons in withdrawn rats may be partly mediated by TRPV1. Altogether, our data suggest that TRPV1 channels in the LHb contribute to pain, anxiety, depressive and relapse-like behaviors, common morbidities seen during alcohol withdrawal, suggesting the physiological and pathological importance of centrally located TRPV1 channels.

Disclosures: J. Ye: None. **D. Gregor:** None. **W. Zuo:** None. **R. Fu:** None.

Poster

122. HCN, TRP, and Other Ion Channels

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Program#/Poster#: 122.15/D61

Topic: B.04. Ion Channels

Support: Norwegian Research Council - NRC

Title: Dual adrenergic modulation of HCN channels in hippocampal and neocortical pyramidal neurons

Authors: *J. F. STORM, C. KLAUS, N. HAGGER-VAUGHAN, H. HU
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Abstract: HCN channels are known to play important roles in regulation of synaptic integration and dendritic signaling in cortical pyramidal neurons, and to be regulated by a variety of neuromodulators. We investigated the influence of alpha- and beta-adrenergic receptor agonists in hippocampal and neocortical pyramidal neurons in rat brain slices. Previously our group found that the beta receptor activation functionally upregulates HCN channels (h-current, Ih) in CA1 hippocampal pyramidal neurons via cyclic AMP, in a direct manner, independently of protein kinase A (Pedarzani and Storm, PNAS, 1995). We have now also tested the effects of the beta adrenergic agonist isoprenaline (10 µM) in layer 5 neocortical pyramidal neurons, and find that it increased the HCN channel-mediated sag in response to hyperpolarizing current pulses in some cells. In contrast, we found that the alpha adrenergic agonists clonidine (10 µM) strongly reduced the HCN channel-mediated sag, and increased the input resistance in CA1 hippocampal pyramidal neurons, as others have previously found in neocortical pyramidal neurons. These effects were mimicked and occluded by the HCN channel-blocker ZD7288 (10 µM), suggesting an alpha-adrenergic downregulation of HCN channel activity. Clonidine also strongly reduced the peak amplitude of a summed series of evoked excitatory synaptic potentials (EPSPs) in CA1 cells. The latter effect of clonidine on EPSPs was accompanied by an increase in paired-pulse facilitation, and was not occluded by the HCN channel-blocker ZD7288, suggesting that it was mediated by a presynaptic inhibition of glutamate transmission, rather than by dendritic HCN channels. These results suggest that two opposite types of adrenergic modulation of HCN channels coexist in at least some neocortical hippocampal pyramidal neurons: HCN channels activity is suppressed via alpha receptors, while being enhanced via beta receptors and cyclic AMP. These may provide diverse means for specific regulation of distal dendritic signaling and synaptic integration in pyramidal neurons.

Disclosures: **J.F. Storm:** None. **C. Klaus:** None. **N. Hagger-Vaughan:** None. **H. Hu:** None.

Poster

122. HCN, TRP, and Other Ion Channels

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Topic: B.04. Ion Channels

Support: CIHR MOP111211

NSERC RGPIN386664

Title: Modulation of *Aplysia* neuroendocrine cell cation channels by phosphoinositide signalling

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Abstract: In the marine snail, *Aplysia californica*, reproduction is initiated when the neuroendocrine bag cell neurons secret egg-laying hormone during a profound change in their electrical and biochemical properties, known as the afterdischarge. The afterdischarge has two distinct phases: an initial fast-phase, with spiking at ~5 Hz, and a long slow-phase, with firing at ~1 Hz. A voltage-gated, non-selective cation channel, similar to transient receptor potential (TRP) channels, provides drive for the depolarization associated with the afterdischarge, and is modulated by several signaling cascades active in the slow-phase. When the afterdischarge is triggered by cholinergic synaptic input, phospholipase C (PLC) is activated to hydrolyze phosphatidylinositol-4,5-bisphosphate (PIP_2) into diacylglycerol (DAG), a protein kinase C (PKC) activator, and inositol trisphosphate (IP_3). We previously reported that a DAG analogue, OAG, activates a large, inward current that is enhanced by IP_3; this is similar to certain TRP channels in other systems. To examine the underlying mechanism in *Aplysia*, we investigated the effect of PLC activation, as well as exogenous OAG and IP_3 on cation channel activity and voltage-dependence in excised, inside-out patches from cultured bag cell neurons. Pretreatment with the PLC activator, m-3M3FBS, left-shifted cation channel voltage-dependence; this was also observed with OAG, but not to the same extent. When neurons were treated with both OAG and IP_3, the voltage-dependence was further left-shifted, closer to that of m-3M3FBS. Activating PKC with phorbol ester pretreatment did not affect voltage-dependence, consistent with DAG/OAG interacting directly with the channel. Applying m-3M3FBS onto the cytoplasmic face of excised patches increased open probability, suggesting PLC may be physically linked to the channels. Blocking PLC activity with the inhibitor, U-73122, ablated the m-3M3FBS-induced increase in channel activity. OAG transiently elevated open probability when bath applied to excised patches; however, co-application of IP_3 prolonged the OAG-induced response. Regulation of cation channel activity by the products of PIP_2 hydrolysis appears to involve lipid-protein interactions, and was more potent than by PIP_2 itself, which modestly both left-shifts voltage-dependence and increases channel activity. PIP_2 breakdown products released during the afterdischarge serve to modulate the cation channel so to temporally control activity throughout the slow-phase.

Disclosures: R.M. Sturgeon: None. **N.S. Magoski:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.17/D63

Topic: B.04. Ion Channels

Support: NIH grant NS086082

NIH grant MH086928

Title: Modeling cellular noxious cold sensation in *Drosophila* sensory neurons

Authors: *N. MAKSYMCHUK, A. A. PATEL, N. J. HIMMEL, D. N. COX, G. CYMBALYUK
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Abstract: Levels of neuronal activation are commonly assessed by changes in intracellular calcium concentration, $[Ca^{2+}]_i$. Noxious cold sensation in *Drosophila* presents a paradox challenging the usability of the $[Ca^{2+}]_i$ as a universal marker for neuronal activation and subsequent behavioral output. A recent study of *Drosophila* larva revealed that noxious cold detection is mediated by the TRP channels Pkd2 and Tprm in class III (CIII) sensory neurons. Activation of these neurons under acute cold triggers a nocifensive full body contraction (CT) behavior and correlates with a rise in $[Ca^{2+}]_i$ in response to declining temperature (Turner et al., 2016). Pkd2 and Trpm channels may contribute to Ca^{2+} influx and are required to mediate CT behavior. Ca^{2+} imaging in CIII neurons mutant for these ion channels reveals a paradox. In contrast to Pkd2 mutants which exhibit reductions in $[Ca^{2+}]_i$ levels in response to acute cold, Trpm mutants exhibit an increase in $[Ca^{2+}]_i$ levels above control and yet still display an inhibition of CT behavior (Turner et al., 2016).

We developed a Hodgkin-Huxley-type model of the cold-sensitive CIII neurons. The model describes interaction of different ionic channels including Pkd2, Trpm, and Ca^{2+} activated K^+ channels (*e.g.* SK) in the neuron. The model produces spiking in response to the temperature changes. It exhibits a dependence of spiking and $[Ca^{2+}]_i$ on temperature. The neuron is silent at room temperature and is spiking when the temperature drops below 18 ^oC. This pattern corresponds to the stereotyped CT behavior. The model of the neuron with disrupted Trpm function assumes that the mutation of Trpm is homeostatically accompanied by a compensatory increase in the number of Pkd2 ion channels and, thus, an increase in the Pkd2 current conductance, which, in turn, leads to an amplified rise of $[Ca^{2+}]_i$ under noxious cold temperatures.

Our model reproduces the experimental results where $[Ca^{2+}]_i$ level increases significantly in Trpm mutants. This higher $[Ca^{2+}]_i$ activates SK current thereby hyperpolarizing the membrane potential and suppressing spiking, which ultimately leads to inhibition of CT behavior. In support of this homeostatic model, experimental analyses of Trpm mutants reveal an average 2 fold increase in Pkd2 mRNA levels relative to controls. Thus, this homeostatic increase of the number of Pkd2 channels could explain the paradox where dysfunction of Trpm is accompanied by the significant increase in $[Ca^{2+}]_i$ and suppression of the stereotyped protective CT response to noxious cold stimuli. The model suggests that cold-evoked CT behavior is finely tuned to an optimal Ca^{2+} level.

Reference:

Turner, H. N., et al., (2016). Current Biology, 3116-3128.

Disclosures: **N. Maksymchuk:** None. **A.A. Patel:** None. **N.J. Himmel:** None. **D.N. Cox:** None. **G. Cymbalyuk:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.18/E1

Topic: B.04. Ion Channels

Title: Structure function characterization of TRPA1 reveals inter-domain interactions critical for channel gating and residues essential for compound binding

Authors: ***W. TSENG**[1], K. M. PADILLA[3], S. HAN[2], V. SHANMUGASUNDARAM[2], K. E. YOGER[3], B. M. ANTONIO[3], D. C. PRYDE[4], A. C. GERLACH[3]
[1]Pfizer, Cambridge, MA; [2]Pfizer, Groton, CT; [3]Icagen, Durham, NC; [4]Curadev, London, United Kingdom

Abstract: TRPA1, a member of the transient receptor potential channel (TRP) family is a primary pain target activated by pungent substances through covalent modification of cysteine residues within its N-terminal ankyrin repeats. Though the biochemistry of reactive cysteines is well defined, the mechanism of how covalent modification translates to channel activation remains unknown. Here we hypothesize that upon covalent activation, residues from the S4-S5 linker couple to those from the TRP-like domain resulting in the conformational changes necessary for opening the gate of the channel. Using site-directed mutagenesis of a total of 23 amino acids spanning the entirety of the S4-S5 linker region, we identified two mutations, R852A and E854R, conferring impaired activation by 300 µM cinnamaldehyde while responses to non-covalent pore binders were similar to wild type. This suggests that the N-terminal region of the S4-S5 linker is critical for channel activation by covalent modification, probably through intramolecular coupling between the pre-S1 linker region and the first helix of the TRP-like domain. In another study we mapped the binding site of a novel TRPA1 inhibitor, thiadiazole, to ankyrin repeat #6 in the N-terminus using chimeric constructs. We further narrowed down the binding site of thiadiazole to three critical amino acids, G239, N250, K271, and demonstrated both loss-of-function and gain-of-function activity by mutating to corresponding residues in different species. Together these results reveal novel mechanisms of TRPA1 activation by distinct classes of chemicals, thus strengthening our understanding of TRP channel gating and providing winning by design strategies for ion channel drug discovery.

Disclosures: **W. Tseng:** A. Employment/Salary (full or part-time):; Pfizer. **K.M. Padilla:** A. Employment/Salary (full or part-time):; Icagen. **S. Han:** A. Employment/Salary (full or part-time):; Pfizer. **V. Shanmugasundaram:** A. Employment/Salary (full or part-time):; Pfizer. **K.E. Yoger:** A. Employment/Salary (full or part-time):; Icagen. **B.M. Antonio:** A.

Employment/Salary (full or part-time):; Icagen. **D.C. Pryde:** A. Employment/Salary (full or part-time):; Curadev. **A.C. Gerlach:** A. Employment/Salary (full or part-time):; Icagen.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.19/E2

Topic: D.03. Somatosensation: Pain

Support: Conacyt grant 221660

Title: $Ca_V3.2$ channel regulation by cyclin-dependent kinase 5 in neuropathic pain

Authors: *K. GOMEZ[1], A. VARGAS-PARADA[1], V. GRANADOS-SOTO[3], R. FELIX[2], R. DELGADO-LEZAMA[1]
[1]Fisiologia, Biofisica y Neurociencias, [2]Biología Celular, Cinvestav, Ciudad de Mexico, Mexico; [3]Farmacobiología, Cinvestav, Sede Sur, Ciudad de Mexico, Mexico

Abstract: Low voltage-activated (LVA) T-type Ca^{2+} channels are activated in response to subthreshold membrane depolarizations and represent an important source of Ca^{2+} influx near the resting membrane potential. These channels regulate diverse physiological events including neuronal excitability, and have been linked to several pathological conditions such as absence epilepsy, cardiovascular diseases and neuropathic pain. It is acknowledged that CaM-dependent protein kinase II (CaMKII) regulates the activation of these channels, and that protein kinases A and C (PKA and PKC) increase T-type current density. Recently, it has been suggested that T-type channels are also a substrate of the cyclin-dependent kinase 5 (Cdk5), a neuron-specific, proline-directed serine/threonine kinase that forms a complex with its activator p35. The Cdk5/p35 complex seems to phosphorylate $Ca_v3.2$ channels, increasing their trafficking to the plasma membrane. Interestingly, during peripheral nerve injury, an upregulation of $Ca_v3.2$ channels and Cdk5 may occur in the dorsal root ganglia (DRG) and in the spinal dorsal horn (SDH), which has been correlated with allodynia. Likewise, intrathecal administration of roscovitine, a Cdk5 inhibitor, relieves mechanical allodynia in neuropathic pain animal models. Therefore, we sought to determine whether Cdk5 regulates $Ca_v3.2$ channel functional expression in rats with neuropathic pain induced by L5/L6 spinal nerve ligation (SNL). To this end, we determined the effect of the Cdk5 inhibitor olomoucine alone and after the application of mibefradil on the compound action potential (cAP) recorded on the L4 and L5 spinal nerves, as well as the 50% paw withdrawal threshold. In addition, we evaluated the expression of the $Ca_v3.2$ channels, Cdk5, p35 and p25 (a truncated form of p35) in L3/L4 and L5/L6 DRGs. We found that SNL did not modify $Ca_v3.2$ channel total expression but upregulated Cdk5 and p35 expression in L5/L6 DRGs without any significant changes in L3/L4 DRGs. Likewise, we observed the presence of p25 in L5/L6 DRGs 1-14 days after SNL, while p25 expression

decreased in L3/L4 DRGs 7 days after SNL. Furthermore, intrathecal injection of olomoucine alleviated mechanical allodynia and decreased the area of the cAP of the C component in spinal nerve ligated animals, while the application of olomoucine after blocking T-type Ca^{2+}channels with mibefradil did not affect the area of the cAP, suggesting an effect of olomoucine on the T-type Ca^{2+}channels. Our results suggest that T-type channel activity is increased by Cdk5-mediated phosphorylation after SNL contributing to long-lasting tactile allodynia.

Disclosures: K. Gomez: None. **A. Vargas-Parada:** None. **V. Granados-Soto:** None. **R. Felix:** None. **R. Delgado-Lezama:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.20/E3

Topic: B.04. Ion Channels

Support: HL133505

Title: 5-HT_3 activation enhances spontaneous but not evoked glutamate release from solitary tract afferents

Authors: *J. A. FAWLEY, M. W. DOYLE, M. C. ANDRESEN
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Abstract: Myelinated (A-fiber) and unmyelinated (C-fiber) cranial visceral afferents synapse in the nucleus of the solitary tract (NTS). C-fiber afferent terminals express the calcium-permeant channel, transient receptor potential vanilloid type 1 receptor (TRPV1). All glutamate release is calcium dependent. Action potentials evoked by solitary tract (ST) stimulation trigger similar glutamatergic EPSCs via voltage-dependent calcium channels in both TRPV1+ and TRPV1- ST afferents at all second order NTS neurons. However, TRPV1+ serves as an independent calcium source and ST afferents with this receptor additionally discharge asynchronous EPSCs after bursts of ST stimuli and have higher rates of spontaneous EPSCs compared to TRPV1- afferents. The different forms of glutamate release (evoked, spontaneous and asynchronous) have distinct calcium sources that can be selectively modulated, consistent with separate vesicle pools within the same terminal[1]. The 5-HT_3 receptor is a calcium-permeant channel that is heterogeneously expressed in ST afferents and impacts central autonomic regulation. Here, we tested whether 5-HT_3 receptor activation altered afferent synaptic transmission of TRPV1+ and TRPV1- afferents. In horizontal hindbrain slices, the minimal time-invariance of the arrival time of ST-evoked EPSCs (jitter, SD of the latency, <200 μs) identified second order NTS sensory neurons. TRPV1 expression was verified using resiniferatoxin (RTX, 2 nM). In 65% of TRPV1+ afferents, the 5-HT_3R selective agonist, m-chlorophenyl biguanide hydrochloride (PBG 1-10 μM) increased

sEPSC rates by an average of 250% indicating predominant co-expression of 5-HT_3 with TRPV1 (n = 15/23). Likewise, in most TRPV1- afferents (n = 2/3), 5-HT_3 activation increased sEPSC rate an average of 300%. Surprisingly, 5-HT_3 activation failed to alter ST-EPSC amplitudes at times when sEPSC rates were maximally enhanced suggesting a differential enhancement of spontaneous glutamate release but no change in the probability of evoked glutamate release from either afferent type. In ~50% of responsive neurons, 5-HT_3 delayed ST-EPSC latency and increased synaptic failures, consistent with 5-HT_3R activation that induced depolarization block of ST axonal conduction. These data suggest that calcium entering through presynaptic 5-HT_3 receptors increases the probability of release from the spontaneous but not the evoked vesicle pool.

[1]Fawley et al., 2016, J Neurosci. PMID 27559176

Disclosures: **J.A. Fawley:** None. **M.W. Doyle:** None. **M.C. Andresen:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.21/E4

Topic: B.04. Ion Channels

Title: Identification of transient receptor potential melastatin 2 (TRPM2) agonists and antagonists using a cell-based high throughput screening assay

Authors: *M. S. SANE, J. WANG, W. WANG, B. D. MOYER, N. GAVVA
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Abstract: Transient receptor potential melastatin 2 (TRPM2) is a voltage-independent, Ca^{2+}-permeable, and thermosensitive cation channel that contributes to variety of cellular processes such as insulin release, neuronal growth, inflammation and cytokine production. TRPM2 is expressed in neutrophils, insulin secreting pancreatic beta cells, microglia and neurons; however, the precise physiological role(s) of TRPM2 in these cells/tissues is incompletely understood. Intracellular second messengers such as ADP, ribose-ADP, NADP and Ca^{2+} activate TRPM2 under physiological conditions. Moreover, activation of TRPM2 by reactive oxygen species has been implicated in cardiovascular as well as neurodegenerative diseases. The gain of function TRPM2 cSNP rs1556314, which imparts the amino acid change N543Q in cytoplasmic N-terminal domain of the protein, is associated with increased risk for bipolar disorder in familial and genome-wide association studies. Despite the availability of a structure for TRPM2, potent and selective activators and inhibitors have not been reported. Thus, the aim of the present study was to develop a cell-based high throughput screening assay to identify TRPM2 selective modulators. We used an inducible T-Rex-CHO TRPM2 cell line for primary screening of 9,600 compounds at 10 μM and measured calcium levels following stimulation with the synthetic

agonist methylnitronitrosoguanidine (MNNG) using a Fluorescent Imaging Plate Reader (FLIPR). In agonist screening mode, activation induced by an EC_{80} concentration of MNNG served as a positive control in each screening plate. Compounds activating TRPM2 were tested against parental CHO cells at 10 µM to eliminate non-selective compounds. We found 22 compounds devoid of activity in parental CHO cells and selective for TRPM2 activation. In antagonist screening mode, 544 compounds showed > 80% inhibition of MNNG activation. We will present potency and selectivity data for the top TRPM2 modulators identified in this screening campaign. In conclusion, we have identified TRPM2 activators and inhibitors which can potentially be used to decipher the role of TRPM2 function in normal and diseased states.

Disclosures: M.S. Sane: None. **J. Wang:** None. **W. Wang:** None. **B.D. Moyer:** None. **N. Gavva:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.22/E5

Topic: D.03. Somatosensation: Pain

Support: R21NS077330

R01NS087033

Title: STIM1 plays a role in nociception and peripheral sensitization

Authors: *D. WEI[1], Y. MEI[1], Y. TIAN[1], H. HU[2]
[1]Dept. of Pharmacol. and Physiol., [2]Pharmacologe and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: STIM1 is a key component of store-operated Ca^{2+} channels (SOCs), which are highly Ca^{2+} selective cation channels that mediate Ca^{2+} entry in many different cell types. We have shown that inhibition of SOCs by a non-selective inhibitor, YM-58483, strongly attenuates capsaicin (an agonist of TRPV1)-induced acute pain as well as formalin-induced nociceptive behavior. Our previous results have also demonstrated that the SOC family is expressed in DRG neurons. However, whether STIM1 plays a role in nociception and peripheral sensitization remains to be determined. Here we show that ML-9, a pharmacological inhibitor for STIM1, strongly attenuated the thapsigargin (TG)-induced translocation of STIM1 to the plasma membrane and diminished SOC entry in DRG neurons. We also found that administration of ML-9 significantly reduced the first phase and second phase of formalin-induced nociceptive behavior when injected peripherally or intrathecally, respectively. Moreover, intraplantar administration of ML-9 attenuated capsaicin-induced acute pain. To further investigate the role

of STIM1 in nociception and peripheral sensitization, we made conditional knockout (KO) mice in which STIM1 is deleted in vesicle glutamate transporter (VGLUT2) positive neurons. Our data revealed that TG-induced Ca^{2+} influx was significantly decreased in DRG neurons from STIM1 KO mice. Noxious stimuli induced-acute pain and both the first and second phases of formalin-induced nociceptive behavior were drastically attenuated in STIM1 KO mice. More importantly, STIM1 expression and SOCE in neurons were significantly increased in the ipsilateral side of L4-L5 DRGs from carrageenan-injected mice. Taken together, our findings suggest that STIM1 contributes to SOCE in DRG neurons and plays an important role in nociception and peripheral sensitization.

Disclosures: D. Wei: None. **Y. Mei:** None. **Y. Tian:** None. **H. Hu:** None.

Poster

122. HCN, TRP, and Other Ion Channels

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 122.23/E6

Topic: D.03. Somatosensation: Pain

Support: R01NS087033

R21NS077330

Title: Critical role of Orai1 in modulation of nociception

Authors: *H. HU[1], Y. DOU[2], Y. TIAN[2]
[1]Pharmacologe and Physiol., [2]Pharmacol. and Physiol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Store-operated calcium channels (SOCs) are calcium-selective cation channels that play an important role in autoimmune and inflammatory diseases. We have demonstrated that SOCs are expressed in spinal cord dorsal horn neurons and inhibition of SOCs attenuates chronic pain. However, the role of SOCs in central nervous system disorders, including pain, remains poorly understood. Orai1 is a key component of SOCs. Our previous study showed that Orai1-mediated modulation of A-type potassium currents and neuronal excitability is ERK-dependent in dorsal horn neurons. The ERK signaling cascade plays a key role in pain plasticity. In the present study, we sought to explore the potential role of Orai1 in the modulation of pain hypersensitivity. Using Orai1 knockout (KO) mice, we demonstrated that Orai1 deficiency markedly decreased noxious stimuli-induced acute pain, and nearly eliminated the second phase of formalin-induced nociceptive behavior. Moreover, Orai1 KO mice showed a significant decrease in Complete Freund's adjuvant, carrageenan and Substance P-induced nociception. Decreased pain hypersensitivity in Orai1 KO mice was associated with ERK-dependent

modulation in the spinal cord dorsal horn. Taken together, these results indicate that Orai1 is involved in central sensitization and plays a critical role in pain behavior through the ERK signaling pathway. Our findings advance our understanding of the mechanisms underlying Orai1-mediated modulation of nociception and provide insight into pain plasticity.

Disclosures: H. Hu: None. **Y. Dou:** None. **Y. Tian:** None.

Poster

123. Structural Plasticity: Spines

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 123.01/E7

Topic: B.08. Synaptic Plasticity

Support: Grant-in-Aid for Young Scientists B (16K18376)

Title: Super-resolution imaging of synaptic proteins

Authors: *N. KOGANEZAWA, T. SHIRAO
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Abstract: Dendritic spines are postsynaptic responsive regions of excitatory synapses and play an important role in synaptic transmission and plasticity. Several proteins which localize within dendritic spines are known to regulate spine morphology and function, and the subcellular distribution changes of these proteins are thought to be important factors of synaptic plasticity. In conventional fluorescence microscopic images, however, it was hard to detect at which part of spines these proteins exist, although some studies using electron microscopy indicate distribution of the proteins within a spine. To reveal nanoscale organization of synaptic proteins, we used stochastic optical reconstruction microscopy (STORM) in this study. Relatively small numbers of fluorophores are activated randomly and it allows temporal separation of individual molecules, resulting in super-resolution images. We first observed localizations of several synaptic proteins such as drebrin, synapsin I and PSD-95 during resting state using primary cultured hippocampal neurons. Drebrin is an actin-binding protein which forms stable F-actin and is highly accumulated within dendritic spines. Synapsin I associates with the synaptic vesicles and presents at presynaptic site. PSD-95 is a scaffold protein and exists at postsynaptic site. In the STORM images, drebrin accumulated in the center of the spine heads and synapsin I localized face to face. Both drebrin and PSD-95 localized within the dendritic spines, but they have slightly different distribution pattern. It is known that NMDA receptor activation induces a bidirectional shift in subcellular distribution of drebrin. Thus we further observed localization changes of these proteins after glutamate stimulation. Drebrin changed its distribution from dendritic spine heads to the dendritic shafts after the glutamate stimulation and tended to be scattered along the dendrite. While synapsin I and PSD-95 did not change their distribution

pattern. These results indicate that the stable core of F-actin in the central region of the spine head is decorated by drebrin under resting condition. Drebrin exodus from spine heads after glutamate stimulation suggests loss of stable F-actin and dynamic F-actin is thought to be predominant. Dynamic localization changes of drebrin indicate importance of drebrin in spine plasticity.

Disclosures: **N. Koganezawa:** None. **T. Shirao:** None.

Poster

123. Structural Plasticity: Spines

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 123.02/DP02/E8 (Dynamic Poster)

Topic: B.08. Synaptic Plasticity

Support: NIH Grant 610510800060039275

Title: A synaptic role of FKBP5, a genetic risk factor for stress-related psychiatric disorders

Authors: ***K. MYCZEK**[1], H. YAMAZAKI[2], I. OZSAN[1], M. MARTIN-DE-SAAVEDRA[1], C. R. ZACCARD[1], P. PENZES[1]
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Abstract: The development of psychiatric disorders, such as depression, post-traumatic stress-disorder, and bipolar disorder has been shown to be associated with alterations in neuronal structure and function, particularly in the cerebral cortex. While recent large scale clinical genomics studies have identified genetic risk factors for psychiatric disorders, the functional analysis of these risk genes and their encoded proteins is the next major challenge. Among these, FKBP5, encoding FK506 binding protein 5, is a prominent genetic risk factor for stress-related mood and anxiety disorders, including depression and post-traumatic stress-disorder. However, the mechanisms by which FKBP5 contributes to disease pathogenesis are not well understood. While a role for FKBP5 as a glucocorticoid receptor co-chaperone has been shown, additional mechanisms have not been investigated in the brain. We hypothesized that FKBP5 may also function at synapses, sites relevant for the pathogenesis of psychiatric disorders. By utilizing an in vitro model of stress and primary rodent cortical cultures, we have found independent effects of stress and FKBP5 on neuronal morphology. Furthermore, our super-resolution microscopy and live cell imaging techniques have revealed a unique synaptic role of FKBP5. We also explore dendritic spine and sub-spine dynamics, revealing unique effects on cellular plasticity not otherwise observable using traditional fixed cell techniques. Further studies investigating the molecular pathways involved in FKBP5-mediated synaptic processes can provide insight into disease pathogenesis and lead to novel therapeutic strategies.

Disclosures: **K. Myczek:** None. **H. Yamazaki:** None. **I. Ozsan:** None. **M. Martin-de-Saavedra:** None. **C.R. Zaccard:** None. **P. Penzes:** None.

Poster

123. Structural Plasticity: Spines

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 123.03/E9

Topic: B.08. Synaptic Plasticity

Support: NRF-2012R1A1A2042145

Title: Asef1 regulates dendritic plasticity through Staufen interaction

Authors: *H. KIM, J.-Y. OH, K.-S. YOO
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Abstract: Guanine-nucleotide exchange factors (GEFs) play important roles in many cellular processes, including the regulation of the structural plasticity of dendritic spines. A GEF protein, *adenomatous polyposis coli* (APC)-stimulated guanine nucleotide-exchange factor 1 (Asef1, ARHGEF4) is highly expressed in the nervous system. However, the function and regulation of Asef1 have not been investigated in neurons. Here, we show that Asef1 blocks Staufen-mediated synaptic delivery of PSD-95 by directly interacting with Staufen, suggesting that Asef1 negatively regulates the synaptic localization of PSD-95 in the excitatory synapse. Furthermore, neuronal activity facilitates the dissociation of Staufen from Asef1 in a PI3-kinase signaling pathway-dependent manner, and this dissociation is required for the GEF activity of Asef1. Our data reveal activity-dependent dual roles of Asef1: as a negative regulator for synaptic delivery of PSD-95 and a Cdc42 GEF for regulating actin cytoskeleton, which is regulated by neuronal activity modulating its interaction with Staufen.

Disclosures: **H. Kim:** None. **J. Oh:** None. **K. Yoo:** None.

Poster

123. Structural Plasticity: Spines

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 123.04/E10

Topic: B.08. Synaptic Plasticity

Support: NIH RO1NS062736

AHA 14POST20490122

Title: NMDA receptor signaling mechanisms in activity-dependent spine shrinkage

Authors: *I. S. STEIN[1], J. N. JAHNCKE[2], K. M. ZITO[3]
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Abstract: Dynamic modification of synaptic connectivity following sensory experience is vital for the refinement of brain circuits during learning and memory. The modulation of dendritic spine structure and synaptic strength contributes to this activity-driven rearrangement of neuronal circuits. Notably, the elimination or pruning of excessive and imprecise dendritic spine synapses has been linked to improvements in learning, and increased spine loss has been associated with intellectual disability and behavioral impairment. The shrinkage and elimination of spines can be driven by glutamatergic activity patterns that lead to the long-term depression (LTD) of synaptic strength. This synaptic weakening and spine shrinkage requires activation of the NMDA-type glutamate receptor (NMDAR) and has been long thought to depend on Ca2+-influx through the receptor. Intriguingly, recent findings demonstrate that block of Ca2+-influx through the NMDAR did not prevent spine shrinkage and LTD induction, instead supporting a model whereby conformational changes of the NMDAR signaling complex are sufficient to induce spine shrinkage and synaptic weakening, independent of NMDAR-mediated Ca2+-influx. Using two-photon glutamate uncaging and time-lapse imaging in combination with pharmacological manipulations, we have shown that activation of p38 MAPK is necessary for this non-ionotropic NMDAR signaling and activity-dependent spine shrinkage. Currently, we are defining the required p38 MAPK signaling pathway and investigating the role of other synaptic plasticity signaling molecules in this non-ionotropic NMDAR-dependent signaling towards spine shrinkage. Results from these experiments will lead to a better understanding of the mechanisms that drive the shrinkage and elimination of dendritic spines normally during neuronal circuit refinement and which are substantially dysregulated in disease.

Disclosures: I.S. Stein: None. **J.N. Jahncke:** None. **K.M. Zito:** None.

Poster

123. Structural Plasticity: Spines

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 123.05/E11

Topic: B.08. Synaptic Plasticity

Support: DFG FOR 2419

ERC-2016-STG 714762

Title: Long-term integration of plasticity and activity at identified Schaffer collateral synapses

Authors: *M. PULIN, T. G. OERTNER, J. S. WIEGERT
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Abstract: Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission change synaptic pathways in an activity-dependent manner. However, although such changes seem to be stable over days, it is less clear how plasticity affects individual synapses over time. We showed previously that LTD preferably leads to elimination of low release probability synapses, suggesting that weight adjustments affect synaptic lifetime. Thus, reversible changes in the connectivity of neuronal networks induced by LTP or LTD could be made permanent through synapse elimination and stabilization. During normal experience, synapses may be exposed to multiple plasticity-inducing events and their persistence may therefore directly depend on the precise sequence of potentiation and depression. However, we do not know how ongoing activity, potentiation and depression are integrated over time at individual synapses to regulate their persistence. We combine optogenetic and chemogenetic tools to tightly control activity at identified Schaffer collateral synapses in organotypic hippocampal slice cultures. All-optical induction of LTD and LTP in combination with 2-photon calcium imaging allowed us to measure the strength of individual synapses and to follow their fate after depression or potentiation over 7 days. A presynaptic theta-frequency stimulation protocol triggering dendritic calcium spikes resulted in LTP of postsynaptic calcium responses. Although concomitant spine volume increase was not sustained for > 24 h, spine survival was enhanced during the following week. Interestingly, LTP induction 24 h after LTD induction completely reversed the reduction in synaptic lifetime, while the inverse protocol (LTD 24 h after LTP) led to increased elimination. Thus, individual synapses exposed to multiple potentiation and depression events distributed over many hours adjust their probability of survival according to the latest plasticity event. In addition, based on the observation that higher synapse elimination after LTD was associated with low release probability, we tested whether chronically changing activity at identified synapses has an impact on their lifetime. We therefore used chemogenetic silencing to chronically block transmission selectively at functionally identified synapses. Unexpectedly, shutdown of evoked synaptic transmission for 7 days did not alter the lifetime of native synapses, suggesting that reduced transmission alone could not account for increased synapse elimination. In summary, plasticity is required to set the lifetime of synapses, while reduced transmission alone has no effect.

Disclosures: M. Pulin: None. **T.G. Oertner:** None. **J.S. Wiegert:** None.

Poster

123. Structural Plasticity: Spines

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Program#/Poster#: 123.06/E12

Topic: B.08. Synaptic Plasticity

Support: NSFC Grant 31530039

NSFC Grant 31325017

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MOST China Grant 2016YFA0500100

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Title: Postsynaptic endophilin A1 regulates synaptic plasticity and long-term memory

Authors: Y. YANG, Z. GUO, S. DENG, X. DU, S. ZHU, *J.-J. LIU
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Abstract: Endophilin A1 plays multiple roles in synaptic structure and function, including regulation of neurotransmitter release and synaptic vesicle recycling, dendritic spine morphogenesis and synapse formation. Although members of the endophilin A family are functionally redundant in uncoating of clathrin-coated vesicles at the presynaptic site and autophagosome formation, role(s) of postsynaptic endophilin A1 in synaptic structure and function remains to be explored. Here we report that postsynaptic ablation of endophilin A1 impairs synaptic plasticity. Endophilin A1 is predominantly expressed in CA1 and CA3 pyramidal cells in the hippocampus. Knockout (KO) of endophilin A1 in mouse causes deficits in hippocampus-dependent learning and memory. The enlargement of dendritic spine head and increase in postsynaptic AMPAR numbers are also impaired in KO neurons during chemically induced LTP, which can be rescued by overexpression of endophilin A1 but not endophilin A2. These results reveal a postsynaptic role of endophilin A1 distinct from that of other endophilin A members in structural and functional plasticity of dendritic spines.

Disclosures: Y. Yang: None. **Z. Guo:** None. **S. Deng:** None. **X. Du:** None. **S. Zhu:** None. **J. Liu:** None.

Poster

123. Structural Plasticity: Spines

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Support: National Brain Research Program KTIA_NAP_13-2-2014-0018

OTKA K81934

New National Excellence Program of the Ministry of Human Capacities

Gedeon Richter Centenarium Foundation

Title: Caskin scaffold protein regulates dendritic spine morphology, learning and memory

Authors: *K. SCHLETT[1,3], N. BENCSIK[1], S. PUSZTAI[1], A. FEKETE[4], S. BORBÉLY[1], V. KIS[2], A. SZUCS[1,3], L. BUDAY[4]
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Abstract: Caskin (CASK interacting protein), a scaffold protein possessing ankyrin repeats, SH3 and tandem SAM domains and a proline-rich C-terminal region, is abundantly expressed in the brain and is located at synapses. While CASK mutations have been implicated in neurological diseases, little is known about how the two Caskin isoforms, Caskin1 and 2 influence synaptic functions.
We have investigated the effects of Caskin1 on dendritic spine morphology. Confocal and electron microscopy of cultured neurons revealed that overexpressed Caskin1 was present predominantly in the somatodendritic region of neurons and was enriched especially in dendritic spine heads, colocalizing with the postsynaptic scaffold protein PSD95 and Shank2. Immunoprecipitation further confirmed that Shank2 and Caskin1 localize within the same complex. Importantly, overexpression of Caskin1 increased the amount of more mature, mushroom-shaped dendritic spines in the expense of filamentous spines of cultivated neurons. We also examined the spine morphology of Caskin1,2 double knock out (CaskinKO) mice and their heterozygous littermate controls in the hippocampus CA1 str. radiatum by electron microscopy. The area and the perimeter of the investigated dendritic spines were similar between the two genotypes, but the length of the PSD and also the PSD/area ratio were significantly decreased in CaskinKO mice, indicating a lack of proper localization of the postsynaptic density proteins.
LTP induction in hippocampal slices was impaired in CaskinKO animals while basal synaptic activity appeared to be normal. Behavioural tests showed that the lack of Caskin did not influence general locomotory activity but Caskin KO mice had deficits in memory formation, including novelty recognition and spatial memory. Taken together, our results prove a previously unnoticed postsynaptic role for the Caskin scaffold protein, regulating dendritic spine morphology and learning abilities possibly via interacting with members of the PSD.

Disclosures: **K. Schlett:** None. **N. Bencsik:** None. **S. Pusztai:** None. **A. Fekete:** None. **S. Borbély:** None. **V. Kis:** None. **A. Szucs:** None. **L. Buday:** None.

Poster

123. Structural Plasticity: Spines

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Program#/Poster#: 123.08/F2

Topic: B.08. Synaptic Plasticity

Support: NIH Grant

Title: BDNF Met prodomain eliminates spines and alters fear extincion circuitry

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Abstract: Single nucleotide polymorphism in Brain Deived Neurotrophic Factor gene that leads to a change of Val in position 66 into Met results in a formation of a Met66 prodomain ligand. We show that this ligand affects synaptic plasticity in vitro and causes changes in fear extinction circuitry in vivo during periadolescent phase, thus making carriers of this SNP succeptible to developing post traumatic stress disorder.

Disclosures: J. Giza: None. **F. Lee:** None. **B. Hemsptead:** None. **J. Kim:** None. **A. Anastasia:** None.

Poster

123. Structural Plasticity: Spines

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Topic: B.08. Synaptic Plasticity

Support: National Institute on Aging, National Institute of Heath 1R01AG047296-01A1

Pilot COBRE on Aging and Regenerative Medicine A50886G5 5P20GM103629-03

Louisiana Board of Regents RCS (LEQSF(2016-19)-RD-A-24)

Louisiana Board of Regents Graduate Research Fellowship LEQSF (2013-18)-GF-17

Tulane Newcomb Undergraduate Research Grants

Title: Bundled whisker stimulation causes age-dependent bidirectional structural plasticity of L5 apical tuft dendritic spines

Authors: *R. L. VOGLEWEDE[1,3], K. M. VANDEMARK[3], A. R. DEWITT[3], M. D. HEFFLER[3,4], E. H. TRIMMER[3], R. MOSTANY[2,3]
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Abstract: Previous research shows that aged mice display an elevated dendritic spine turnover ratio in the apical tuft of L5 pyramidal neurons of the primary somatosensory cortex (S1) when compared to young adult mice (Mostany et al., 2013). This suggests that synapses within this cortical area of aged animals are less stable at baseline conditions, in the absence of manipulation.
The current project explores how this elevated turnover of synaptic connections in the somatosensory cortex of aged animals affects the synaptic reorganization that follows a sensory manipulation designed to induce structural plasticity. Using chronic in vivo two-photon imaging through a 4mm cranial window, we followed apical tuft dendrites of layer V pyramidal neurons within S1 of Thy1-eGFP-M male mice from two age sets: young adult (aged 3-5 months) and aged (18-22 months). We employed continuous bundled whisker stimulation with a piezoelectric actuator at 8Hz for 10 minutes/day over 4 days. Mice were imaged over 46 days spanning before, throughout, and following sessions of bundled whisker stimulation. Imaging sessions occurred every 4 days as well as every 24 hours during the peri-stimulation period to examine these changes with better temporal resolution.
We observe an acute increase (from 0.13 ± 0.01 to 0.17 ± 0.01 spines/µm; $p<0.0001$) in the dendritic spine turnover ratio immediately following whisker stimulation in young adult mice. For aged mice, we observe an opposite effect: a decrease in turnover ratio (from 0. 17 ± 0.01 to 0.13 ± 0.01 spines/µm; $p=0.0001$) following their initially higher baseline. The age-gap in turnover ratio between the groups disappears following the whisker stimulation (0.12 ± 0.01, young adult vs. 0.13 ± 0.01, aged, spines/µm, days 16-20), suggesting aged mice experience a form of synaptic stabilization following this sensory manipulation that returns the turnover ratio to young adult levels. Further analysis aims to explore how these bidirectional, age-dependent responses may serve as a compensatory or homeostatic mechanism that the aged brain employs during sensory processing.

Disclosures: R.L. Voglewede: None. **K.M. Vandemark:** None. **A.R. DeWitt:** None. **M.D. Heffler:** None. **E.H. Trimmer:** None. **R. Mostany:** None.

Poster

123. Structural Plasticity: Spines

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Louisiana BOA RCS LEQSF(2016-19)-RD-A-24

Title: Dendritic spine density, dynamics, and morphology of layer 5 pyramidal neurons in the young and aged forepaw area of primary motor cortex

Authors: *A. M. DAVIDSON[1], H. MEJÍA-GÓMEZ[2], M. JACOBOWITZ[3], R. MOSTANY[3,2]
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Abstract: It is well-established that unfortunately the healthy, aged brain frequently shows deficits in motor control, causing otherwise healthy individuals to struggle with coordination and fine motor skills, but the neuroanatomical basis for this decline is not known. Here we use long-term *in vivo* two photon microscopy and a cranial window procedure in order to investigate structural differences in the primary motor cortex of young and aged mice that may underlie these age-related deficits. Using male and female GFP-M transgenic mice which sparsely express GFP under the *Thy*-1 promotor allows for repeated imaging of the same dendritic fragments belonging to GFP-expressing layer 5 (L5) pyramidal neurons. L5 pyramidal neurons of the primary motor cortex are of particular interest because their dendrites process input from many cortical areas and their axons carry the summed output of the cortex to the spinal cord in order to direct voluntary muscle action. The apical dendritic tufts of these cells are of interest to us because the dendritic spines they house are the primary sites of excitatory input into these cells. These dendrites have been imaged chronically, over a period of one month, in young (3-5 months) and aged (20+ months) mice in order to determine dendritic spine density, dynamics, and morphology. Our data suggest that L5 pyramidal neurons of the aged motor cortex exhibit increased dendritic spine density, with 0.75 spines/µm in the aged group compared with 0.59 spines/µm in the young group ($p < 0.05$). Dendritic spine turnover is also elevated in the aged motor cortex, with 0.29 spines/µm gained or lost in the aged group compared with 0.19 spines/µm in the young group ($p < 0.05$). Significant differences in dendritic spine stabilization are also evident, with an increased rate of stabilization of new dendritic spines in the short term (over 4 days) but a decreased rate in the longer term (over 30 days). Because the information processing ability of the cortex is reliant on its level of connectivity, these structural differences may have important functional implications that contribute to age-related cognitive impairments, which our lab is currently investigating.

Disclosures: A.M. Davidson: None. **H. Mejía-Gómez:** None. **M. Jacobowitz:** None. **R. Mostany:** None.

Poster

123. Structural Plasticity: Spines

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Topic: B.08. Synaptic Plasticity

Support: Deutsche Forschungsgemeinschaft (DFG) Research Grant RA689/12-1

Title: Diazepam impairs structural plasticity of dendritic spines in somatosensory cortex independent of $GABA_A$ receptor activation

Authors: *Y. SHI[1,2,3,4], M. M. DOROSTKAR[1,3,4], G. RAMMES[5], J. HERMS[1,3,4]
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Abstract: Diazepam is a medication of the benzodiazepine family that typically produces sedative effects. It is commonly used for insomnia, anxiety, and muscle spasms therapies. However, prolonged diazepam use causes cognitive impairment and is thought to be a modifiable risk factor for developing Alzheimer's disease (AD). Dendritic spines, the critical structural correlates for cognitive performance, are highly dynamic. Alterations of dendritic spine structural plasticity are observed under specific conditions such as prolonged central nervous system (CNS) drug treatment or AD development. Up to date, whether and how diazepam alters structural plasticity of dendritic spines remain barely understood. To explore the impact of diazepam treatment on structural plasticity of dendritic spines, we performed long-term *in vivo* two-photon imaging of apical dendrites of layer V pyramidal neurons in Thy1-eGFP transgenic mouse somatosensory cortex. Both male and female mice aged 4-5 months were assigned to the vehicle and treatment groups, which received daily vehicle (0.5% CMC-Na, i.g.) or diazepam (5 mg/kg, i.g.) treatment. Treatment started 16 days after the first imaging time point and was continued over 28 days. Our results showed that diazepam strongly impaired structural plasticity of dendritic spines. Spine density in the diazepam treated mice was significantly reduced compared to the vehicle group, as a consequence of decreased spine formation and increased spine elimination. Given that diazepam primarily binds to $GABA_A$ receptor benzodiazepine binding site in the CNS, we next chose flumazenil, a selective benzodiazepine receptor antagonist, to clarify whether $GABA_A$ receptor-mediated signaling pathway was responsible for the diazepam impaired spine plasticity. Interestingly, pharmacologically blocking $GABA_A$ receptors by flumazenil failed to abolish the structural synaptic alterations induced by diazepam. These results collectively suggest that prolonged diazepam treatment induces impaired structural

plasticity of dendritic spines of layer V pyramidal neurons, which is independent of $GABA_A$ receptor-mediated signaling pathway.

Disclosures: Y. Shi: None. **M.M. Dorostkar:** None. **G. Rammes:** None. **J. Herms:** None.

Poster

123. Structural Plasticity: Spines

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Topic: B.08. Synaptic Plasticity

Support: National Institute on Aging, National Institute of Heath 1R01AG047296-01A1

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Louisiana Board of Regents RCS (LEQSF(2016-19)-RD-A-24)

Louisiana Board of Regents Graduate Research Fellowship LEQSF (2013-18)-GF-17

Tulane Newcomb Undergraduate Research Grant

Title: Age-related changes in dendritic spine volume and morphology in the primary somatosensory cortex after sensory stimulation

Authors: *K. VANDEMARK[1,2], R. L. VOGLEWEDE[2,1], R. MOSTANY[2,1,3]
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Abstract: Previous research (Mostany et al., 2013) shows that aged mice display an elevated dendritic spine turnover ratio in the apical dendritic tuft of Layer V pyramidal neurons of the primary somatosensory cortex (S1) when compared to young adult mice, suggesting that synapses of aged animals are less stable over time. The current study from our laboratory explores the functional implications that less stable, more plastic synaptic connections within the aged cortex may have for learning and memory as animals undergo a sensory experience (whisker stimulation) designed to induce plasticity (Megevand et al., 2009, Gambino et al., 2014). Using chronic in vivo two photon imaging through a cranial window, we followed apical tuft dendrites of layer V pyramidal neurons within S1 of Thy1-eGFP-M male mice of two ages: young adult (3-5 months) and aged (18-22 months). Mice were imaged before and following sessions of stimulation, occurring from days 8–11, and that consisted of continuous bundled whisker stimulation with a piezoelectric actuator at 8 Hz for 10 minutes a day over these 4 days. Imaging sessions occurred every 4 days (days 0 - 20) to observe changes in spine dynamics. Our current morphological analysis allows for the measurement of three spine types: thin,

stubby, and mushroom. This analysis includes the relative proportions of these spine types on a given imaging day and spine tracking, making it possible for us to measure spines' persistence and quantify the transitions from one spine type to another before and after stimulation. While we do not find differences in mean mushroom spine head volume between groups, we do observe a greater fraction (24.4%) of mushroom spines transitioning into other morphologies following stimulation in aged mice when compared to the young adult group (18.3%), coupled with a smaller overall fraction (29.2%, aged versus 42.5%, young adult) of mushroom spines making up the total spine population after stimulation. This intersectional analysis aims to combine spine volume, morphology, and persistence to explore how these age-dependent responses interact following sensory processing.

Disclosures: K. Vandemark: None. **R.L. Voglewede:** None. **R. Mostany:** None.

Poster

123. Structural Plasticity: Spines

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Program#/Poster#: 123.13/F7

Topic: B.08. Synaptic Plasticity

Support: NSF GRFP

Title: Effects of response learning on medium spiny neurons and immature neurons in the dorsal striatum

Authors: *B. A. BRIONES, V. D. TANG, A. E. HAYE, E. GOULD
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Abstract: The dorsal striatum (dStr) has been linked to spatial navigation and response learning, two parallel systems that initiate engagement of either deliberate or habitual behaviors. In the rodent, the dorsolateral striatum (DLS) is required for response learning acquisition and the dorsomedial striatum (DMS) is required for spatial-place learning acquisition. Previous studies have shown dendritic spines in the dorsal striatum are responsive to several different kinds of experiences, and that new cells with neuronal characteristics are added to this brain region in adulthood. Investigating the effects of response learning on these forms of structural plasticity would fill in the gaps in our knowledge of how the striatum responds to experience and may provide clues about the mechanisms underlying response learning acquisition. To investigate this question, we used DiI labeling and immunohistochemistry to analyze dendritic spines, primary sites of excitatory synapses, on striatal medium spiny neurons (MSNs), as well as immature neurons in the dorsal striatum. We analyzed dendritic spines exclusively on MSNs that were positive for the immediate early gene (IEG) zif268, an indirect marker of neuronal activation, and found no effect of response learning on overall dendritic spine density or size. However, our

results did show an increase in response learning MSN spine subtypes compared to cage controls, suggesting an enriched environment effect. Taken together, this experiment suggests that activated MSNs are more similar to one another in both control and response learners than are non-activated MSNs. Last, we detected significantly fewer cells that expressed the marker of immature neurons doublecortin (DCX) in response learners and maze controls compared to caged controls, suggesting a stress effect. While our results suggest that response learning does not produce robust differences in dendritic spines or immature neuron number in the DLS, it remains unknown whether non-activated MSNs would show such changes.

Disclosures: **B.A. Briones:** None. **V.D. Tang:** None. **A.E. Haye:** None. **E. Gould:** None.

Poster

123. Structural Plasticity: Spines

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Support: JSPS KAKENHI Grant 15K18333

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JSPS KAKENHI Grant 26221001

JST CREST JPMJCR1652

AMED Strategic Research Program for Brain Sciences

Title: A super-sensitivity of dopamine D2 receptor signaling for structural plasticity of dendritic spines

Authors: *S. YAGISHITA, Y. IINO, R. NAKAZATO, H. KASAI
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Abstract: Reward or punishment transiently activates or suppresses dopamine (DA) activity to drive conditioned learnings. Previously, we have shown that reward-related phasic activation of DA reinforces spine enlargement of D1-spiny projection neurons (SPNs) in the nucleus accumbens (NAc) within the time window of 0.3 - 2 s (Yagishita et al., Science, 2014). In contrast, punishment-related transient suppression of DA has been considered to affect D2-SPNs. However, cellular mechanisms for the detection of subsecond decrease in DA concentration (DA dip) remains poorly understood. Here, we tested whether single dendritic spines detect optogenetically reproduced DA dips for the structural plasticity. We stimulated DA terminals which expressed ChR2 with 5 Hz blue light pulse in acute slices of mouse NAc to maintain

stable concentration of DA. Then, we inserted pause period during tonic DA excitation to mimick DA dip, a transient decrease in DA concentration which was confirmed by amperometry. Next, structural plasticity of single spines from virally labelled D2-SPNs was induced by spike-timing dependent plasticity (STDP) protocol with two-photon glutamate uncaging followed by action potentials. We found that STDP stimulation induced spine enlargement in the presence but not in the absence of agonist of adenosine A2A receptor (A2AR), which is expressed specifically in D2-SPNs. This spine enlargement was inhibited by 5 Hz tonic DA, suggesting that the D2R and A2AR competitively balance the plasticity. This inhibition of spine enlargement by tonic DA was circumvented when a DA dip as short as 0.4 s was applied immediately after STDP. Thus, D2-SPNs detect the subsecond DA dip for the plasticity, suggesting that D2R is super-sensitive to a subtle change in DA concentration. Furthermore, we tested whether this plasticity mechanism is relevant to conditioned learning. Recently we revealed optogenetic excitation of glutamatergic input to NAc served as conditioned stimulus (CS) to form association with reward in head-fixed mice (unpublished). Using this technique, we found that A2AR antagonist disrupted extinction learning caused by optogenetic stimulation of synaptic inputs to NAc. These results suggest that D2-SPNs detect the DA dip at single dendritic spine for spine enlargement and extinction learning through the mechanism involving D2Rs. Since D2R is the major target of antipsychotic drugs and genetically related to schizophrenia, we will further investigate the molecular mechanism underlying the super-sensitivity of D2R using a genetically-encoded cAMP sensor in single-spine resolution.

Disclosures: **S. Yagishita:** None. **Y. Iino:** None. **R. Nakazato:** None. **H. Kasai:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Topic: B.11. Epilepsy

Support: NIH Grant 5R01NS074785

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NIH Grant 5R37MH071739

NIH Grant F30 NS100293

FACES: Finding a Cure for Epilepsy and Seizures

Title: Cannabidiol (CBD) interrupts a novel positive feedback loop involving LPI-GPR55 signaling to restore excitatory-to-inhibitory coordination

Authors: *E. C. ROSENBERG[1], M. BAZELOT[3], A. SALAH[1], B. WHALLEY[3], O. DEVINSKY[2], R. W. TSIEN[1]
[1]Neurosci. and Physiol., [2]Neurol., NYU Sch. of Med., New York, NY; [3]Pharm., Univ. of Reading, Reading, United Kingdom

Abstract: Recent clinical trials suggest that cannabidiol (CBD), a non-psychoactive component of cannabis, can reduce seizure frequency in several forms of pediatric epilepsy. While the exact anti-seizure mechanism of CBD is unclear, one leading hypothesis predicts that CBD inhibits the actions of an endogenous membrane phospholipid, lysophosphatidylinositol (LPI), at the G-protein coupled receptor, GPR55. CBD blocks LPI-mediated increases in presynaptic Ca^{2+} and vesicular release at excitatory axon terminals, thus reducing excitability at glutamatergic synapses (Sylantyev et al. 2013). However, new findings suggest that CBD may reduce seizures in interneuron-specific forms of epilepsy such as Dravet Syndrome (Devinsky et al. 2015), prompting renewed exploration of CBD, LPI, GPR55 in inhibitory networks and in epilepsy. Using a multidisciplinary approach, we found that LPI produces distinct pre- and postsynaptic effects at excitatory and inhibitory synapses. Consistent with prior reports of a presynaptic target, 4 μM LPI acutely increased mEPSC frequency in CA1 hippocampus, an effect blocked by pre-treatment with 1μM CBD and absent in GPR55 KO mice. However, prominent somatic GPR55 immunostaining in CA1 pyramidal neurons suggested an additional postsynaptic action of LPI and GPR55. Consistently, 4 μM LPI reduced inhibitory postsynaptic strength, $GABA_AR$ γ_2 Ser327 phosphorylation, and γ_2 subunit expression. These effects were absent in GPR55 KO mice and prevented by pre-treatment with 1μM CBD. Taken together, these results suggest that LPI increases the excitatory/inhibitory ratio in hippocampal neuronal networks by a dual mechanism: enhancing excitatory transmission and attenuating inhibition. We predict that LPI will elevate excitability in the hippocampal CA3-CA1 microcircuit through changes in short-term plasticity and spike throughput, thereby leveraging beneficial effects of CBD blockade. We further observe that LPI-mediated increases in mEPSC frequency are potentiated in hippocampal slices from animals rendered epileptic following lithium-pilocarpine induced epileptogenesis. Consistent with this finding, acute kainic-acid induced seizures elevated membrane-bound GPR55 expression. Together, these results predict a potential positive feedback loop in which seizures elevate GPR55 expression, augmenting the effect of LPI and its seizure-promoting effects on excitatory / inhibitory coordination. We hypothesize that CBD exerts a potential anti-seizure effect by blocking the actions of LPI at both excitatory and inhibitory synapses, and that GPR55 may represent a potential biomarker for epilepsy.

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Program#/Poster#: 124.02/F10

Topic: B.11. Epilepsy

Support: GW Pharmaceuticals Grant 66346

Title: Involvement of $GABA_AR$ and NMDAR in the anticonvulsant actions of cannabidiol - studies in human cortex and rodent entorhinal cortex *In vitro*

Authors: *B. HENLEY[1], R. A. GRAY[2], S. GREENHILL[1], I. M. STANFORD[1], G. L. WOODHALL[1]
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Abstract: Phytocannabinoid derivatives of *Cannabis Sativa* are an exciting new class of anticonvulsants and one, cannabidiol (CBD), has displayed potent anticonvulsant properties in recent clinical trials in patients with two forms of childhood onset epilepsy. Here, we investigated the anticonvulsant effect of 30μM CBD using whole-cell patch clamp recording in Layer II of the medial entorhinal cortex of adolescent male *status epilepticus* experienced (SE) and age-matched control (AMC) Wistar rats (50-100g) *in vitro*. The Reduced Intensity Status Epilepticus (RISE) model of acquired epilepsy was used to induce epileptogenesis. Data were also collected from *ex vivo* human tissue (HT), resected in pediatric neurosurgery from patients with drug-refractory epilepsy. The effects on normalized inhibitory charge transfer (NICT) of spontaneous inhibitory post-synaptic currents (sIPSCs) were compared between AMC and SE populations. In SE rats, CBD was found to significantly increase NICT (mean = 134.858, p=0.0053), while in AMC rats the effect was not significant (mean = 115.32, p=0.2661). Elucidation of the mechanism of action focused on $GABA_AR$ and NMDAR involvement. Using only SE rats, 500nM flumazenil was perfused via bath onto slices, to inhibit the benzodiazepine binding site of GABAAR. The addition of flumazenil before CBD, caused a significant decrease in NICT (mean = 2.54, p = 0.0015), which was then recovered upon addition of CBD (mean = 72.62). When CBD was added before flumazenil however, the action of flumazenil was blocked (mean = 116.5). These data suggest that CBD is able to bind to $GABA_ARs$ and exert a benzodiazepine like effect, but does not bind to the classical benzodiazepine site, most likely binding to an allosteric modulatory site. This hypothesis is supported by radioligand binding data performed by GW and recent work (Bakas et al., 2017). NMDARs meanwhile were inhibited competitively using 100nM MK801. The addition of MK801 previous to CBD was able to fully block the effects seen using CBD alone (MK801 mean = 87.07, plus CBD mean = 82.17). When CBD was added previous to MK801 the inhibition remained (CBD mean = 139.8, plus MK801

mean = 120.7). Taken together, these data suggest the possible involvement of $GABA_A$Rs and NMDARs in the anti-epileptic mechanism of CBD.

Disclosures: **B. Henley:** A. Employment/Salary (full or part-time):; GW Pharma. 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.; GW Pharma. **R.A. Gray:** A. Employment/Salary (full or part-time):; GW Pharma. **S. Greenhill:** None. **I.M. Stanford:** None. **G.L. Woodhall:** 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.; GW Pharma.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.03/F11

Topic: B.11. Epilepsy

Support: European Union Seventh Framework Programme (FP7/2007 – 2013; grant agreement 602130)

The Royal Society

Title: Anti-seizure and biophysical effects of microRNA-134 knockdown

Authors: *G. MORRIS, S. SCHORGE
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Abstract: MicroRNAs (miRs) are ~22 nt non-coding RNA sequences, which typically suppress gene expression through specific binding to target mRNAs. MiR-134 is upregulated in multiple models of epilepsy and influences the density and volume of dendritic spines. MiR-134 knockdown protects against seizures, though it is unclear how. We explored the effects of miR-134 knockdown in naïve ex vivo brain slices. Adult male Sprague Dawley rats were given intracerebroventricular injections of an 'antagomir' against miR-134 (ant-134). Rats completed a novel object location test at least 24 hours after injection and brain slices were prepared 2-4 days post-surgery. Anti-epileptic effects were tested by seizure challenge with 9 mM K^+. Intrinsic biophysical neuronal properties were tested with whole cell voltage and current clamp. Recorded neurons were filled with biocytin for posthoc anatomical reconstruction. Ant-134 significantly delayed the onset of epileptiform activity in 9 mM K^+ by an average of 182 s relative to control (n = 9 control slices; 11 ant-134 slices; Mann Whitney U test p = 0.002). There was a tendency towards a faster action potential rising slope in CA1 pyramidal neurons (PNs) though this did not

pass significance after correction for multiple comparisons (control: 179 ± 82 mV/ms, n = 6 neurons; ant-134: 251 ± 18 mV/ms, n=7 neurons; independent samples t test p = 0.043, α=0.025). All other tested biophysical properties in CA1 PNs were unaffected. These data will be compared with ongoing experiments on CA3 biophysics, neuronal morphology and rats' performance in the spatial memory test. We have replicated the anti-seizure effects of ant-134 in an acute model of epileptiform activity, showing that the anti-epileptic effect can be produced in healthy brain tissue. We saw little or no effect of ant-134 on many biophysical parameters, suggesting it mediates seizure resistance through relatively specific mechanisms, which could be valuable for future translation to the clinic. This work was supported by the EpimiRNA consortium and a fellowship from the Royal Society.

Disclosures: G. Morris: None. **S. Schorge:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Program#/Poster#: 124.04/F12

Topic: B.11. Epilepsy

Title: Bumetanide enhances the pharmacological effect of phenobarbital on behavioral level, in an animal model of temporal lobe epilepsy

Authors: *C. A. MANTELLERO[1,2], J. AMARO[2], M. BORQUEZ[2], A. OCAMPO[2], J. VALDES[2], P. ROJAS[1]
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Abstract: Temporal lobe epilepsy (TLE) is the most common type of refractory epilepsy to drug treatment. The most important structure involve is the hippocampus, because has been related to the cognitive impairment observed in patients.In epileptic conditions neurons have an increased excitability due in part to a change in GABA from inhibitory to excitatory. This is due to a change in the direction of electrochemical gradient of Chloride, whose concentration is maintained by co- transporters KCC2 and NKCC1. Models of acute seizures have shown that NKCC1 is highly expressed explaining the high intracellular chloride. In a model of neonatal seizures, Bumetanide, an specific NKCC1 inhibitor, in combination with Phenobarbital shows a significant improvement in seizure control.
The aim of this work is to study in an animal model of TLE the refractoriness to a GABAA agonist Phenobarbital, and if in combination therapy with Bumetanide enhances its pharmacological effect decreasing the number of seizures, and a behavioral level reversing cognitive impairment.
Male 7 weeks old Sprague Dawley rats were administrated with Pilocarpine to induce Status Epilepticus (SE), and after two weeks they have spontaneous seizures. Animals were

administrated with Phenobarbital (N=20), to assess the refractoriness of this treatment. After 2 weeks the rats that do not respond to pharmacological treatment with phenobarbital are separated into 3 groups, 1 group continues the treatment with Phenobarbital (N=5), other group with Bumetanide (N=5), and other with both; bumetanide and phenobarbital (N=5) during two weeks.Electroencephalogram (EEG) recordings were performed before and after the treatment with Phenobarbital and after the last treatment in each group, to quantify alterations in epileptiform activity.
The results show all pharmacological treatments decreases the number of seizures and no potentiation was observed in combination therapy.To determine the effect of these treatments on cognitive impairment, object recognition test were performed, to evaluate episodic memory. Open field was conducted to evaluate anxiety, and last, social interaction was studied to evaluated sign that suggesting depression. The results show that the combination therapy improves behavioral parameters.
These findings support the idea that NKCC1 participates in TLE, and probably high doses of bumetanide is necessary to potentiate the effect of Phenobarbital an electroencephalographic level.

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

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Alfred P. Sloan Foundation Fellowship in Neuroscience

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Title: Indigenous bacteria of the gut microbiota mediate antiseizure effects of the ketogenic diet

Authors: *C. OLSON, H. E. VUONG, J. M. YANO, Q. Y. LIANG, D. J. NUSBAUM, E. HSIAO
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Abstract: The high-fat and low-carbohydrate ketogenic diet (KD) is an effective therapeutic for refractory epilepsy, but the molecular mechanisms underlying its antiseizure effects remain unclear. Diet is a primary stimulus shaping the relative composition of the gut microbiota, which is causally linked to changes in host metabolism and physiology. Here, we study the role of the gut microbiota in mediating seizure protection of the KD. We demonstrate that the gut microbiota is necessary and sufficient for seizure protection in response to the KD in the 6-Hz psychomotor seizure assay and in spontaneous tonic-clonic seizures for the Kcna1-/- transgenic line. Enrichment and gnotobiotic co-colonization with KD-associated restores seizure protection lost during microbiome depletion. Additionally, selective colonization or probiotic treatment utilizing KD-associated bacteria sufficiently raises the seizure threshold for mice consuming control diet (CD). KD- and microbiota-dependent alterations in colonic lumenal, serum, and hippocampal metabolomic profiles correlate with seizure protection including reductions in γ-glutamylated ketogenic amino acids and an elevated hippocampal GABA/glutamate ratio. We demonstrate that reducing γ-glutamylation in non-protected mice sufficiently confers seizure protection and that the KD and cross-feeding between KD-associated microbes inhibits the process of γ-glutamylation. Overall, this study reveals a novel role for specific gut bacterial interactions in modulating seizure susceptibility. Future studies will analyze the role microbiome-gut-brain circuits in microbial modulation of host cognition.

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Topic: B.11. Epilepsy

Support: NINDS grant #1U54NS079202

Title: Effects of nerve agent antidote treatment in tetramethylenedisulfotetramine-induced status epilepticus

Authors: *D. ZOLKOWSKA, A. DHIR, M. A. ROGAWSKI
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Abstract: The current standard of care initial treatment for organophosphate (OP) nerve agent poisoning is the muscarinic antagonist atropine and the oxime acetylcholinesterase reactivator pralidoxime chloride (2-PAM), which may be administered using a CHEMPACK Mark 1 Kit available in the National Strategic Stockpile. This 2-component autoinjector system (2 mg atropine; 600 mg 2-PAM) allows emergency medical services (EMS) personnel to respond

rapidly to emergencies in the field. At the time a victim of nerve agent poisoning comes to the attention of the EMS first responder, the nature of the neurotoxicant is not likely to be known. Victims may receive treatment for OP agents irrespective of the nature of the nerve agent to which they have been exposed. Convulsant GABA-A receptor antagonists are a second important class of chemical threat agents. Specifically, the National Institutes of Health considers the GABA-A receptor antagonist tetramethylenedisulfotetramine (TETS) to be a high priority threat agent. Here we determined the impact of treatment with atropine and 2-PAM on TETS induced SE and lethality in an attempt to assess whether inadvertent administration of these agents is potentially problematic. Mice were pretreated with a single dose of riluzole (10 mg/kg, IP) and 10 min later received a lethal dose of TETS (0.2 mg/kg, IP). Riluzole does not inhibit TETS-induced SE but does protect against the immediate lethal effects of TETS in mice. Atropine (0.3 mg/kg, IM), 2-PAM (100 mg/kg, IM) or combinations of the 2 agents were administered 10 min after TETS injection. Animals were observed for 1 h after TETS injection and checked for mortality up to 7 days. Atropine and 2-PAM at a dose equivalent by allometric scaling to the doses included in Mark 1 Kit conferred opposite effects on mortality in TETS SE. Atropine injected alone increased long-term survival from 0% in vehicle group to 16% in animals with TETS SE without other treatment. 2-PAM significantly accelerated death inasmuch as 100% animals died within a mean 2.5 min after IM administration compared with vehicle group where no animals died within 2.5 min, 17% died within 1 h and 100% died within 24 h. Lower doses of 2-PAM (2.5-5 mg/kg, IM) injected alone did not accelerate the time of death or affect long-term survival. When co-administered with atropine, 2.5 and 5 mg/kg of 2-PAM decreased the time to mortality such that 37.5 and 50%, respectively, died within 1 h. Our results demonstrate that atropine alone at a human equivalent dose reduces mortality in the mouse TETS SE model and might be beneficial as a treatment agent. By contrast, 2-PAM accelerated mortality in mice and could be potentially harmful for victims of TETS poisoning.

Disclosures: D. Zolkowska: None. **A. Dhir:** None. **M.A. Rogawski:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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GINOP (2.3.2-15-2016-00018)

EFOP (3.6.1-16-2016-00008)

Title: Long-term evolution of absence epilepsy in Long-Evans rats and their closed loop interruption using transcranial electric stimulation

Authors: *G. KOZAK[1], A. BERENYI[1,2]
[1]Univ. of Szeged, Szeged, Hungary; [2]Neurosci. Inst., New York Univ., New York, NY

Abstract: Epilepsy affects 1% of the population worldwide. Despite the development of drug therapies, still one-third of the patients remain unresponsive to the currently available anti-epileptic drugs. Therefore, to find the possible break points of epileptic networks, a deeper mechanistic insight is required into the evolution of the epileptic seizures. Closed-loop transcranial electrical stimulation (TES) may be a promising alternative solution for patients with pharmaceutically intractable seizures, as it does not require cellular modification of neurons to be effective, it is applicable intermittently, and it is less invasive compared to deep brain stimulation. It is long known that Long-Evans rats are showing the electrophysiological and behavioral symptoms of absence epilepsy, in the form of spontaneously emerging, rapidly generalizing, synchronous spike-and-wave (SW) episodes. Their high spontaneous seizure rate makes them an ideal model to investigate the seizure - stimulus interactions of closed loop TES intervention, but still there are many questions about the exact ictogenesis of this particular strain. Therefore the goal of this study was to further explore the translation of closed-loop TES for treatment of epilepsy and to describe the long-term evolution of absence epileptic seizures in chronically implanted Long-Evans rats. Here we show that unsupervised closed-loop TES in rats can consistently interrupt seizures for 6 weeks and has the potential to control seizure activity up to 4 months (longest periods examined). On-demand TES significantly reduced the time spent in seizure and the individual seizure durations, although significantly higher seizure rate was observed during the treatment. The 6 week long stimulation had no residual adverse effects on the electrophysiologic characteristics of the brain after the termination of the treatment and did not induce glial remodeling in the brain. Additionally, in our control animals we could follow the course of ictogenesis from a virtually seizure-free condition to chronic epilepsy and we characterized some key electrophysiological change of the brain dynamics during the development of the disease.

Disclosures: G. Kozak: None. **A. Berenyi:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.08/G4

Topic: B.11. Epilepsy

Support: Science Foundation Ireland: 13/SIRG/2098

Title: The purinergic P2Y1 receptor as a new target to treat status epilepticus and prevent seizure-induced brain damage

Authors: *M. ALVES, A. SANZ-RODRIGUEZ, E. LANGA, D. HENSHALL, T. ENGEL
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Abstract: Epilepsy is a chronic neurological disease characterized by recurrent seizures. Despite the existence of numerous AEDs, 30-40% of patients do not respond to treatment, showing the urgent need for novel therapeutic strategies. ATP, important signaling molecule in the CNS, has emerged as a potential contributor to seizures. Purinergic P2Rs (ionotropic P2XR and metabotropic P2YR) are expressed in the brain and activated by ATP. The majority of studies in epilepsy have been focus on the P2XRs; however P2YRs are now emerging as a new potential target. P2Y1R have been shown to be strongly expressed in astrocytes, where they contribute to the propagation of Ca^{2+} waves. However, the functional role of P2Y1R during seizures is poorly understood.
P2Y1R expression after SE and its effects on seizures were studied using two mouse models of epilepsy. Seizures were induced by intra-amygdala KA or intraperitoneal pilocarpine injections. P2Y1R expression was analyzed in the hippocampus after SE in mice. In addition, specific P2Y1R ligands were administrated into the ventricle after seizure induction and electroencephalography was recorded to assess seizure severity. Procedures were approved by the relevant Research Ethics Committees of the RCSI.
Protein levels of P2Y1R were up-regulated in the hippocampal subfields after SE, mainly in DG and CA1. In contrast expression of P2Y1R was reduced in CA3 and is showing reduced reactivity in the mossy fibers. In the KA model, our results revealed in mice post-treated with P2Y1R agonist MRS2365 an increase of seizure severity, neuronal death and inflammation, while post-treatment with P2Y1R antagonist MRS2500 decreased seizure severity, neuronal death and inflammation. The same results were observed in the pilocarpine model, ruling out model-specific effects. In conclusion, P2Y1R inhibition might be a good approach for the treatment of SE and prevention of seizure-induced brain damage.

Disclosures: M. Alves: None. **A. Sanz-Rodriguez:** None. **E. Langa:** None. **D. Henshall:** None. **T. Engel:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: B.11. Epilepsy

Support: Teva's National Network of Excellence in Neuroscience (NNE) Scholarship

Title: Harnessing genome scale metabolic modeling for the prediction of novel drug-targets for the treatment of hyperactivity associated with neurological disorders

Authors: *N. GONEN[1,2], B. STYR[2], I. VERTKIN[2], I. SHAPIRA[2], I. SLUTSKY[1,2], E. RUPPIN[3]
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Abstract: Elevated neuronal activity in the hippocampus is the hallmark of epilepsy and conditions that confer risk for Alzheimer's disease (AD), including amnestic mild cognitive impairment (MCI). Hippocampal hyperactivity has been shown to be the best predictor of subsequent cognitive decline and conversion to AD. Numerous clinical trials targeting Aβ have shown negligible progress or failure in AD patients. Notably, recent studies suggest that anti- Aβ antibodies are ineffective in improving circuit's dysfunctions and hyperactivity. Thus, identifying mechanisms underlying neuronal hyperactivity is critical for prevention of MCI-to-AD conversion and treatment of currently pharmacoresistant forms of epilepsy. To address this problem, we performed genome-scale metabolic modeling (GSMM) of hippocampal gene-expression data of MCI patients and epilepsy animal models. Based on the GSMM analysis, we identified convergent drug-target – mitochondrial dihydroorotate dehydrogenase (DHODH) enzyme - predicted to rescue metabolic states and neuronal hyperactivity in epilepsy and MCI upon inhibition / knockdown. Utilizing multi-electrode-arrays for long-term monitoring of spiking activity in neural networks and intracellular electrophysiology, we found that inhibition of DHODH enzyme by Teriflunomide or DHODH knockdown trigger a profound reduction in the mean firing rate of hippocampal networks. Teriflunomide-induced firing inhibition did not dependent on *de novo* pyrimidine synthesis. These inhibitory effects were stable during several days of Teriflunomide application. These results emphasize the capacity of MTA-based GSMM analysis to guide the discovery of metabolic drug targets reversing neuronal hyperactivity associated with numerous neurological disorders. Based on our study, we propose DHODH inhibition as a novel promising strategy for treatment of pharmacoresistant types of epilepsy and MCI in an attempt to prevent MCI-to-AD progression.

Disclosures: N. Gonen: 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.; Supported by Teva's National Network of Excellence in Neuroscience scholarship. **B. Styr:** None. **I. Vertkin:** None. **I. Shapira:** None. **I. Slutsky:** None. **E. Ruppin:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Topic: B.11. Epilepsy

Support: Albany Medical College

Dinapoli Research Found

The Dake Foundation

Title: Ventral Pallidum deep brain stimulation has potent efficacy for various seizure phenotypes

Authors: *E. MAHONEY[1], A. ZENG[2], W. J. YU[6], M. ROWE[7], S. SAHAI[8], P. J. FEUSTEL[3], E. MOLHO[9], J. G. PILITSIS[4], A. RAMIREZ-ZAMORA[10], D. S. SHIN[5]
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Abstract: Approximately 65 million people worldwide suffer from epilepsy and ~30% of these individuals are refractory to antiepileptic drugs and require alternative treatment options. Vagal nerve stimulation and responsive neurostimulation are 2 currently FDA approved therapies for refractory epilepsy. While these neuromodulatory approaches have improved quality of life and reduced seizure frequency, they fall short of providing seizure freedom to many individuals and have limited utility for generalized seizures. Here, we expand on previous findings and investigate whether ventral pallidum deep brain stimulation (VP-DBS) can be efficacious across different seizure phenotypes. To do so, rats were implanted bilaterally in the VP with stimulating electrodes and unilaterally with a recording electrode in the somatosensory S1 cortex. We found that VP-DBS (50Hz, 300µA, 90 µs pulse width) even after generalized seizures emerged decreased generalized seizure frequency from 17.8 ± 3.9 to 7.4 ± 1.8 and total duration from 2496.0 ± 844.9 to 510.1 ± 132.9 sec. The transition to brainstem seizures was prevented in almost all animals. VP-DBS immediately after rats exhibited their first partial forebrain seizure did not affect the frequency of partial seizures, but reduced total partial seizure duration from 271 (238-379.5) to 53.5 (10.5-77.8) (lower-upper interquartile range) seconds. This timed stimulation also reduced the number and frequency of emerging secondarily generalized seizures. If VP-DBS was turned on prior to pilocarpine administration, the appearance of partial seizures was prevented in almost all animals. To elucidate the neural network underlying VP-DBS efficacy, we assessed changes in cFos immunoreactivity with or without VP-DBS. VP-DBS decreased hyper-excitability of many forebrain and brainstem structures. Lastly, VP-DBS had potent efficacy in the pentylenetetrazol (PTZ) rat model by delaying generalized tonic-clonic seizures from 168.5± 201.3 (unstimulated) to 1416 ± 1231 seconds (stimulated). Stimulating electrodes placed more laterally in the VP correlated with greater seizure control. In conclusion, our findings posit that VP-DBS can serve as an effective novel neuromodulatory approach for a variety of seizure phenotypes.

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

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Topic: B.11. Epilepsy

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Consolidación y estructuración de Unidades Competitivas. Consellería de Educación Xunta de Galicia

Title: Static magnetic fields reduce epileptic activity in the anaesthetized rat and monkey

Authors: *C. RIVADULLA[1,2,3], M. COLETTI[1], S. Y. PRIETO[1,2,3], J. AGUILA[1], J. R. AGUILAR[4], J. CUDEIRO[1,2,3,5]
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Abstract: There is increasing evidence that Static Magnetic Fields (SMF) reduce cortical activity in both, human and animal models[1,2]. The aim of this work was to study the effect of SMF on epileptic cortical excitability, a condition due to an abnormal increase in neuronal activity.
EEG was continuously recorded in 14 anaesthetized rats, in which epilepsy was induced by the lithium-pilocarpine model: LiCl (127 mg/kg)+ Scopolamine (1mg/Kg) + 2 doses of Pilocarpine (20mg/Kg), and in 1 anaesthetized monkey (Macaca mulatta) with spontaneous epileptic-like activity recorded from primary visual cortex.
Rats were anaesthetized to get a stable slow wave activity showing up and down states. Animals were classified as "*stimulated*" (a magnetic neodymium nickel-plated cylinder, 45mm diameter and 30mm height, magnetic field of 0.5T was placed over the skull before pilocarpine injection), or "*sham*" (a stainless steel replica without magnetic properties was used).
Between 15-30 minutes after the second injection of pilocarpine, EEG changes compatible with epileptic seizures were clearly observable in the sham group: Down states disappeared and were substituted by an abnormal oscillatory activity: Power at 1-4 and 4-8 Hz bands increased. Similar effects were visible in those animals with the real magnet but 1-2 hours later, indicating that SMF were able to slow down the corticographic signs of epilepsy.
In one monkey, we recorded visually-induced paroxysmal activity (epileptic-like activity) in V1.

After application of SMF (30 minutes) over the cortical focus, abnormal activity was clearly reduced: Intensity threshold for induction increased and severity and duration reduced.
These results reinforce the view that static magnets modulate cortical activity and open the door to the future therapeutic use of SMF in epilepsy as a complement to current pharmacological treatments.
1. Oliviero A et al J Physiol. 2011. doi: 10.1113/jphysiol.2011.211953.
2.Aguilá et al Cereb Cortex. 2016 Feb;26(2):628-38. doi: 10.1093/cercor/bhu228

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

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Title: Activity clamp is a new tool to study epileptic mechanims

Authors: *G. LIGNANI, G. MORRIS, M. LEITE, D. KULLMANN, I. PAVLOV, S. SCHORGE
UCL Inst. of Neurolgy, London, United Kingdom

Abstract: Activity clamp is an electrophysiological technique based on dynamic clamp. This technique can be useful to get new insights into anti-epileptic drugs, sodium channel splice variants isolated from the other channels but in an epileptic network activity or to understand the mechanisms of new anti-epileptic treatments.
One application for this technique can be to reconcile the effects of anti-epileptic drugs (AEDs) on individual neurons with their network-level actions. It is unclear why carbamazepine (CBZ) has been reported to increase epileptiform activity in several clinical and experimental studies. To address the underlying mechanisms we used activity clamp, to distinguish the response of individual neurons from network-level actions of CBZ. We first recorded barrages of synaptic conductances from neurons during epileptiform activity, and then replayed them in pharmacologically isolated neurons under control conditions and in the presence of CBZ. CBZ consistently decreased the reliability of the second action potential in each burst of activity. Conventional current clamp recordings failed to reveal this effect. Network modelling showed that a CBZ-induced decrease of neuron recruitment during epileptic bursts can lead to an

increase in burst frequency at the network level, by reducing the refractoriness of excitatory transmission. By combining activity clamp with computer simulations, the present study provides a potential explanation for the paradoxical effects of CBZ on epileptiform activity. Another application for activity clamp is to recreate an epileptic network isolating some ion channels from the others. Neuronal excitability is tightly regulated, requiring rapidly activating and inactivating voltage-gated sodium channels to allow accurate temporal encoding of information. However, the general principles underlying the adaptive significance of alternative splicing for these channels remain poorly understood. Here, we asked whether the functional consequences of this splicing have been preserved in different genes. The consequences of alternate splicing of Nav1.1 and Nav1.2 for neuronal activity depend on whether they are expressed in the cell types where they normally predominate (interneurons or excitatory neurons). Finally activity clamp has been used to show that alternative splicing in Nav1.1 is sufficient to change how rapidly interneurons fire during epileptiform events. While splicing in sodium channels has conserved molecular effects, the impact of the splicing depends on the cell type in which the variants are expressed.

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Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.13/G9

Topic: B.11. Epilepsy

Support: EC grant agreement n. 285827 (EPIXCHANGE)

Title: Unilateral encapsulated cell biodelivery of GDNF into the hippocampus inhibits epileptic seizures in rats

Authors: *E. MELIN[1], A. NANOBASHVILI[3], D. EMERICH[3], J. TORNØE[3], M. SIMONATO[4], L. U. WAHLBERG[3], M. KOKAIA[2]
[2]Lund Univ., [1]Epilepsy Ctr., Lund, Sweden; [3]NsGene, Inc., Providence, RI; [4]Univ. Ferrara, Ferrara, Italy

Abstract: Temporal lobe epilepsy (TLE) is the most common type of epilepsy in adults. This neurological disorder is characterized by complex partial seizures with or without secondary generalization originating from the temporal lobe regions. A variety of pharmacological treatments exist for patients suffering from epilepsy, but systemically administered drugs offer only symptomatic relief and frequently cause unwanted side effects. Moreover, available drugs are ineffective in one third of epilepsy patients. Thus, developing more targeted and effective

treatment strategies for TLE is highly warranted. In our study we used encapsulated cell biodelivery (ECB) to deliver potential anti-epileptic agents directly into the epileptic brain. Specifically, we explored whether local delivery of glial cell line-derived neurotrophic factor (GDNF) in the epileptic focus from ECB devices would suppress already established spontaneous recurrent seizures (SRS) in kainic acid-treated epileptic animals. Our results show that GDNF locally delivered from ECB devices into the seizure focus (i.e., hippocampus) effectively decreases the number of SRS in epileptic rats. Thus, our study indicates that using ECB devices to deliver neurotrophic factors, such as GDNF, focally in the epileptic brain could provide bases for the development of a novel, alternative, treatment for epilepsy.

Disclosures: **E. Melin:** None. **A. Nanobashvili:** A. Employment/Salary (full or part-time):; NsGene, Inc. **D. Emerich:** A. Employment/Salary (full or part-time):; NsGene, Inc. **J. Tornøe:** A. Employment/Salary (full or part-time):; NsGene, Inc.. **M. Simonato:** None. **L.U. Wahlberg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NsGene, Inc. **M. Kokaia:** 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.; NsGene, Inc..

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.14/G10

Topic: B.11. Epilepsy

Support: Pairnomix, LLC

Title: Comprehensive high-throughput drug screening in a cellular model of KCNQ2 epileptic encephalopathy

Authors: *G. R. STEWART[1], C. M. MAHER[1], B. C. GAY[1], J. M. ANDRESEN[1], A. C. GERLACH[2], S. PETROU[3], D. GOLDSTEIN[4]
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Abstract: KCNQ2 epileptic encephalopathy arises due to mutations in the Kv7.2 voltage-gated potassium (K^+) channel. Mutations conferring either a gain or loss of function in KCNQ2 often lead to early infantile epileptic encephalopathy (EIEE) that is usually refractory to conventional anti-epileptic drugs (AEDs). This highlights an acute need to find new therapeutic options for refractory KCNQ2 epilepsy patients. A wild-type or R201C mutant *KCNQ2* gene, along with a copy of the wild-type *KCNQ3* gene, were transfected into CHO cells to generate cell models

capable of producing an M-like K^+ current. Patch clamp evaluation demonstrated a voltage-dependent increase in outward K^+ current for both cell lines. However, the R201C mutation conferred a significant leftward shift in the voltage-current relationship with activation (opening) at lower voltages and a significantly slower deactivation rate compared to wild-type. A rubidium (Rb^+) efflux assay was adapted for high throughput screening (HTS). Exposure to KCl to stimulate channel opening produced a concentration-dependent release of $^{86}Rb^+$ from pre-loaded cells. Co-incubation of either cell line with XE-991, a known KCNQ channel blocker, completely inhibited $^{86}Rb^+$ efflux. Using the $^{86}Rb^+$ efflux assay, wild-type and R201C cell lines were screened against the Prestwick library, a collection of 1,280 drugs that are clinically approved; a panel of AEDs and known ion channel modulators were also included. Of the 1,320 compounds screened at 10 μM, 26 significantly inhibited the wild-type channel and 36 significantly inhibited efflux from the R201C mutant cell line. Interestingly, only two compounds significantly inhibited $^{86}Rb^+$ efflux from both cell lines. Re-screening of the lead compounds in the R201C cell line confirmed their activities in a concentration-dependent manner. The drug with the greatest inhibitory activity against the mutant cell line was paroxetine (SSRI antidepressant; IC_{50} = 6.90 μM; maximum inhibition = 90%); other drugs with potent and significant inhibition of $^{86}Rb^+$ efflux included acitretin (retinoid for psoriasis), norgestimate (steroidal) and hexestrol (a synthetic estrogen). This study demonstrates the utility of precision genetic modeling by replicating an underlying genetic mutation of EIEE in a cell model suitable for HTS. The results identified several compounds that had heretofore not been associated with inhibitory activity against Kv7.2 potassium channels that may hold therapeutic value for KCNQ2 patients with EIEE.

Disclosures: **G.R. Stewart:** A. Employment/Salary (full or part-time):; Pairnomix. 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.; Icagen. **C.M. Maher:** A. Employment/Salary (full or part-time):; Pairnomix, LLC. **B.C. Gay:** A. Employment/Salary (full or part-time):; Pairnomix, LLC. **J.M. Andresen:** A. Employment/Salary (full or part-time):; Pairnomix, LLC. **A.C. Gerlach:** 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.; Pairnomix, LLC. **S. Petrou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pairnomix, LLC. **D. Goldstein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pairnomix, LLC.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.15/H1

Topic: B.11. Epilepsy

Support: National Natural Science Foundation of China 81625006

National Natural Science Foundation of China 31471024

Title: Cox2 inhibition ameliorate seizure susceptibility in a mouse model of autosomal dominant lateral temporal epilepsy

Authors: *Y. SHEN[1], L. ZHOU[2], L. ZHOU[3]
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Abstract: Autosomal dominant lateral temporal epilepsy (ADLTE) is an inherited epilepsy syndrome caused by mutations in *Lgi1* gene. It has been shown that glutamatergic transmission is altered in Lgi1 mutant mice and seizures can be reduced by restoring Lgi1 function. Yet, the underlying mechanism for ADLTE is unclear. Here, we examined intrinsic excitability of pyramidal neurons in the temporal lobe cortex. We found that voltage-gated potassium channel subfamily A (Kv1) were downregulated while cytosolic phospholipase A_2-cyclooxygenase 2 (Cox2) signaling was enhanced in Lgi1-knockout mice. Cox2 inhibition effectively restored dysregulated Kv1.2 and reduced intrinsic excitability of pyramidal neurons. Interestingly, *in vivo* injection with celecoxib, a Food and Drug Administration-approved nonsteroidal anti-inflammatory drug, rescued Kv1.2 and ameliorated neuronal excitability and seizure susceptibility in Lgi1-knockout mice. Together, we propose that Cox2 is a therapeutic target to suppress seizures in ADLTE patients.

Disclosures: Y. Shen: None. **L. Zhou:** None. **L. Zhou:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

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Program#/Poster#: 124.16/H2

Topic: B.11. Epilepsy

Support: Italian Ministry for University and Research (PRIN 2010/2011 to F.C.)

Università Politecnica delle Marche (to FC and GF)

Title: Beyond SV2A: novel insights into levetiracetam's effects

Authors: *D. MARCOTULLI, G. FATTORINI, L. BRAGINA, J. PERUGINI, F. CONTI
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Abstract: Presynaptic proteins are potential therapeutic targets for epilepsy and other neurological diseases. The aim of present study was to verify the hypothesis that chronic treatment with the SV2A ligand levetiracetam (LEV) induces changes in the expression of SV proteins other than SV2A.
Results of western blot (WB) of synaptic fractions (P3) of rat neocortex showed that LEV did not change SV2A and SV2B levels, whereas it reduced the expression of the following vesicular proteins: synaptotagmin (SYT) 1 (to 76±4.44% of controls); SYT2 (to 85.48%±3.21%); SYT9 (to 79.43±4.27%); synapsin (SYN) II (to 69.15±4.78%); SGYR1 (to 76.27±3.67%); SGYR3 (to 73.92±4.56%); VGLUT1 (to 68.81±5.24%), VGLUT2 (to 82.60±5.47%) and VGAT (to 77.33±4.77%). Levels of Rab3a, Rab3c, VAMP1, VAMP2, synaptophysin (SYP) I and SYNI were similar in both groups, indicating that not all vesicular proteins are altered by LEV. Furthermore, the expression of the major plasma membrane proteins participating in neurotransmitter release (i.e., STX1A, STX1B, SNAP23, SNAP25 and Munc18-1) were unchanged compared to controls. No significant change was observed in hippocampus.
Next, we asked whether LEV effects depend on transcriptional, translational or post-translational mechanisms. We therefore measured mRNA levels for LEV-regulated proteins, and analyzed WB of the same proteins in whole cellular proteins content devoid of nuclear fractions (S1). In both neocortex and hippocampus of LEV-treated animals, mRNAs levels and S1 proteins expression were similar in the experimental and control groups, suggesting that LEV-induced changes are in all likelihood due to synaptic terminal-specific post-transcriptional mechanisms.
To gain a deeper insight into LEV effects, we constructed a network of protein-protein interactions (PPI). The analysis of the resulting network identified LRRK2, 14-3-3β and 14-3-3ε as SV2A interactors potentially capable of contributing to LEV effects. Results of RT-PCR showed that mRNA levels coding for LRRK2 and 14-3-3s were not modified by LEV treatment. WB studies showed that 14-3-3β and ε levels were not changed in S1 and P3 samples; and that LRRK2 protein levels were upregulated by LEV (up to 130.08 ± 9.35) in S1 but not in P3 samples, in line with its cellular localization. None of the mRNAs and proteins studied were modified by LEV in hippocampus, confirming the drug's region-specific effect.
The presynaptic proteins regulation induced by LEV reported here suggest that not only SV2A, but the interactions between presynaptic proteins downstream of SV2A, actually mediate LEV effects; and that LRRK2 may play a role in forging the underlying pattern of molecular changes.

Disclosures: D. Marcotulli: None. **G. Fattorini:** None. **L. Bragina:** None. **J. Perugini:** None. **F. Conti:** None.

Poster

124. Epilepsy: Anticonvulsant Therapies: Novel Interventions, Strategies, and Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 124.17/H3

Topic: B.11. Epilepsy

Title: The MTLE mouse model, a predictive model of partial epilepsy for drug discovery

Authors: *C. ROUCARD[1], B. POUYATOS[2], C. BOUYSSIÈRES[3], C. DUMONT[3], B. MANDÉ-NIEDERGANG[3], Y. ROCHE[2], V. DUVEAU[4]
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Abstract: Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of drug-refractory epilepsy. Despite the development of new compounds, more than 30% of patients with epilepsy are still resistant to antiseizure drugs (ASDs). New preclinical strategies are therefore needed to improve ASDs discovery and development. To better understand and treat this syndrome, the use of predictive animal models is mandatory. The MTLE mouse model induced by a unilateral intrahippocampal injection of kainate reproduces most of the morphological and electroclinical features of human MTLE. In this model, epileptic activities are recorded in the epileptic hippocampus, using depth EEG electrodes and are called hippocampal paroxysmal discharges (HPD). Using the MTLE mouse model we have developed a wide range of protocols based on EEG recordings, aiming at evaluating anti-seizure potentials of newly developed compounds. We will present data obtained from our screening protocol, in which we tested several compounds on N=4 MTLE mice. This optimized protocol allows a fast and cost-effective evaluation of the anti-seizure potential of a compound. Hit compound thus identified can be further studied using our dose-response protocols. Classical anti-seizure drugs have been tested using these two protocols. We will show that parallel results have been obtained between the screening protocol and the dose-response effect of 9 of them (published in Duveau et al. 2016). To extent this database, we will present here the example of retigabine from the screening to the dose response protocols. These data show that the MTLE mouse model can be used to screen a library of molecules to identify drugs with anti-seizure potentials. We moreover developed lead validation protocols allowing further characterization and validation of the efficacy of selected drugs, together with comparison to reference drugs.

Disclosures: **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **B. Pouyatos:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Bouyssières:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Dumont:** A. Employment/Salary (full or part-time):; SynapCell SAS. **B. Mandé-Niedergang:** A. Employment/Salary (full or

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.01/H4

Topic: B.13. Demyelinating Disorders

Support: Kent State University

Title: Betaine regulates neuronal mitochondrial activity by modulating methionine metabolites in the cuprizone mouse model of multiple sclerosis

Authors: *N. K. SINGHAL[1], K. ALKHAYER[1], J. SHELESTEK[1], R. CLEMENTS[1], T. G. BOTTIGLIERI[2], E. FREEMAN[1], J. MCDONOUGH[1]
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Abstract: Multiple sclerosis (MS) is a demyelinating and neurodegenerative disorder of the central nervous system. We have previously shown that betaine levels are reduced in MS cortex and are positively correlated with H3K4me3 levels, a histone mark involved in regulating mitochondrial activity, cell metabolism and differentiation. Therefore, the present study was undertaken to evaluate the effect of betaine on mitochondrial associated neuroprotection in the cuprizone mouse model of MS. We administered betaine (1g/kg of mice with drinking water) to mice treated with normal diet and cuprizone (0.3%) diet for six weeks. We measured methionine metabolism intermediates by LC-MS-MS. NAA levels were also measured by HPLC in mice to assess neuronal mitochondrial respiration. We found significant upregulation of SAM/SAH ratio, betaine, methionine, choline and NAA levels in betaine and cuprizone-betaine treated mice as compared to cuprizone only. We also carried out mechanistic studies in primary rat neurons treating with sodium nitroprusside (400 µM) and betaine (1000 µM) to mimic microglial activation of cuprizone mouse model. Gene expression of complex I, complex IV and complex V and respiration increased significantly in betaine and SNP-betaine treated primary neurons as compared to SNP alone. These data suggests that betaine regulates neuronal mitochondrial activity by modulating levels of methionine metabolism intermediates and levels of H3K4me3 methylation.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

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Topic: B.13. Demyelinating Disorders

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Fremantle Hospital Medical Research Foundation

Australian Society for Medical Research

EPSRC (EP/D066654/1)

Title: Characterization of iron loading on myelin; studies in a double mutant mouse model of haemochromatosis

Authors: *M. HEIDARI[1,2], D. M. JOHNSTONE[3], B. BASSETT[2], R. M. GRAHAM[4], C. BETTENCOURT[5], J. F. COLLINGWOOD[6], S. GERAMI[2], M. HOUSE[7], K. MARTIN[2], A. C. G. CHUA[8,9], M. RYTEN[11], H. HOULDEN[5], J. K. OLYNYK[10], D. TRINDER[8,9], E. A. MILWARD[2]

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Abstract: Brian iron dyshomeostasis is associated with various severe neurodegenerative disorders. It is unclear whether brain iron accumulation and consequent degeneration is also a feature of systemic iron loading disorders, such as hereditary hemochromatosis, which can be caused by mutations in the HFE gene or transferrin receptor 2 (TFR2) gene. We have characterized regional distribution of brain iron and whole brain transcriptome alteration in a

mouse model with simultaneous disruption of both the Hfe and Tfr2 genes (Hfe-/-xTfr2mut). Enhanced 3,3'-diaminobenzidine-4HCl Perls' staining was performed on Hfe-/-xTfr2mut brain at 3, 6, 9 and 12 months of age. Iron staining showed strong iron accumulation in choroid plexus and in myelinated fiber tracts in corpus callosum, internal capsule, fornix system and basal ganglia. Cerebral cortex showed only mild iron accumulation and hippocampus was mostly protected from iron loading. These were observed in all ages studied while higher iron accumulation was detected as animals aged. Assessment of brain gene profiles of Hfe-/-xTfr2mut and wildtype mice at three months of age by microarray and real time RT-PCR revealed increases in brain transcripts for important immediate-early transcription regulators, including Fos, Junb and early growth response genes, and decreased transcripts for the transcription repressor Zfp68. Several important genes related to iron metabolism showed decreased brain transcript levels, including the genes for transferrin, transferrin receptor 1, ceruloplasmin and hepcidin. Further microarray data mining revealed that expression of 45 myelin-associated genes including genes related to neurodegeneration with brain iron accumulation (NBIA) disorders also were changed ($p<0.05$). Overlap ($P<0.0001$) of differentially expressed genes in Hfe-/-xTfr2mut brain with human gene coexpression networks suggests iron loading influences expression of NBIArelated and myelinrelated genes coexpressed in normal human basal ganglia. There was overlap ($P<0.0001$) between genes that were differentially expressed in Hfe-/-xTfr2mut brain and postmortem NBIA basal ganglia. Concordance between mouse transcriptome changes and human myelinrelated gene expression networks in normal and NBIA brain suggests potential clinical relevance. Taken together, these suggest that myelin-related systems may be involved in neurodegeneration pathogenesis in early responses to iron loading. These findings may help understand the interrelationships between iron and myelin in more common conditions such as hemochromatosis and multiple sclerosis.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.03/H6

Topic: B.13. Demyelinating Disorders

Support: Boespflug Foundation

Foundation to Fight H-ABC

Title: Myelin, oligodendrocytes and axons in the aged taiep mutant rat

Authors: *D. Z. RADECKI[1], A. B. RADCLIFF[2], M. HEIDARI[2], D. SEBO[2], B. REDFEARN[2], I. D. DUNCAN[2]
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Abstract: The *taiep* rat is an autosomal recessive myelin mutant that has a novel phenotype. In early development, hypomyelination is seen throughout the CNS white matter but there is progressive demyelination with time in the brain, optic nerves and certain tracts of the spinal cord. The underlying cellular abnormality is the accumulation of microtubules in oligodendrocytes (OLs), which we believe is responsible for the failure to develop and maintain normal myelin. We recently identified the mutation in *taiep* as a single point mutation in the *Tubb4a* (p.Ala302Thr), the gene that encodes for the β-tubulin dimer (Duncan et al Annals of Neurol, In Press). Perhaps surprisingly, *taiep* rats live a normal life-span, up to 24-27 months. In this study we compared the white matter status of *taiep* rats at 12 vs. 24 months to examine the long-term effects of the mutation on myelin, axons and glia. We studied these in the optic nerves, and dorsal, lateral, and ventral columns of the spinal cord. In the dorsal column we selected the fasciculus gracilis, fasciculus cuneatus, and corticospinal (CST) tracts as individual structures. In the dorsal column it was shown that the myelin defect preferentially affected small diameter axons, thus the fasciculus cuneatus was always more myelinated than in the other two tracts. Within the fasciculus gracilis and CST, around 5% or less of axons were myelinated at 12 months and this remained unchanged through 24 months. The ventral column showed hypomyelination or lacked a myelin sheath of small diameter axons at 12 and 24 months, though large diameter fibers had maintained a normal g ratio at 24 months. Despite the fact that many axons in the dorsal columns were demyelinated for up to 18 months, there was little evidence of axon loss and the CST in particular contained densely packed, small diameter axons as did the fasciculus gracilis. Although the fasciculus gracilis essentially lacked myelin, there was a clear increase in the OL number, yet this was not seen in the CST. In the fasciculus gracilis and optic nerve the microtubule defect persisted, with OLs having an increased microtubule content. These data suggest that the early hypomyelination is followed quickly by chronic demyelination that peaks by 12 months, with the CNS responding thereafter to the chronic myelin loss. The *taiep* rat therefore provides a unique opportunity to study the long-term
effects of demyelination on axon survival and axon-glial interaction. These aspects of the mutant are currently being explored further.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

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Topic: B.13. Demyelinating Disorders

Support: NMSS RG5239-A-3

NIH R01NS094151

Title: ATF6α activation protects oligodendrocytes against inflammation

Authors: *W. LIN[1], S. STONE[2], S. JAMISON[2], K. MORI[3]
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Abstract: Multiples sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) are inflammatory demyelinating diseases in the CNS. In response to endoplasmic reticulum (ER) stress, activation of the unfolded protein response (UPR), which comprises three branches of signaling pathways, PERK, IRE1, and ATF6α, preserves cell viability and function. Recent studies demonstrate that activation of the PERK branch of the UPR cell-autonomously promotes oligodendrocyte survival in animal models of MS. Evidence suggests activation of the ATF6α branch of the UPR in oligodendrocytes under normal and disease conditions; however, the effects of ATF6α signaling on oligodendrocytes in MS and EAE remain unknown. It has been demonstrated that the presence of IFN-γ, a key pro-inflammatory cytokine in MS and EAE, in the developing CNS induces myelinating oligodendrocyte death and hypomyelination through activation of ER stress in oligodendrocytes. Herein, we found that ATF6α inactivation exacerbated IFN-γ-induced myelinating oligodendrocyte death and hypomyelination in young, developing mice. Moreover, we found that ATF6α inactivation significantly increased the severity of EAE clinical symptoms and aggravated EAE-induced oligodendrocyte loss, demyelination, and axon loss, without affecting inflammation. Thus, these data suggest the protective effects of ATF6α activation on oligodendrocytes in MS and EAE.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

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Program#/Poster#: 125.05/H8

Topic: B.13. Demyelinating Disorders

Title: Neuronal hemoglobin beta regulates levels of H3K4me3

Authors: *K. ALKHAYER[1], J. MCDONOUGH[2], E. FREEMAN[2], N. SINGHAL[2]
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Abstract: Multiple sclerosis (MS) is an inflammatory neurodegenerative disease of the central nervous system (CNS). Previous studies describe a dysregulation of mitochondria and impaired energetics including decreased expression of the nuclear encoded electron transport chain subunit genes in cortical neurons in MS. The presence of hemoglobin mRNA and protein within human and rat neurons in the CNS has been reported in many studies but the function of hemoglobin in cortical neurons is still not clear. We have previously reported that the beta subunit (Hbb) of hemoglobin is expressed in cortical neurons and enriched in pyramidal neurons of deeper cortical layers IV-V . We have also recently shown that levels of Hbb are significantly reduced in nuclear fractions isolated from postmortem MS cortex compared to controls. Overexpressing Hbb in neuronal cell culture increases trimethylation of histone H3 on lysine 4 (H3K4me3). In a previous study we reported that H3K4me3 regulates expression of genes involved in mitochondrial respiration and is reduced in neurons in MS cortex. Taken together these data suggest a link between reduced levels of nuclear Hbb, decreased levels of H3K4me3, and reduced expression of mitochondrial genes in neurons in MS. We have found that Hbb interacts with the KDM5 demethylases that demethylates H3K4me3, in neuronal nuclei. Our data suggest that nuclear localization of Hbb can alter the chromatin landscape and gene expression by inhibiting the KDM5 histone demethylase. The KDM5 histone demethylase requires molecular oxygen (O_2) to oxidize C-H bonds. We hypothesize that Hbb may increase histone H3 methylation by sequestering oxygen away from the KDM5 leading to decreased demethylase activity. Therefore by expressing a mutant -Hbb, unable to bind O_2 ,we will be able to identify the function of Hbb in inhibiting KDM5. Our data suggest that Hbb can support neuronal respiration by regulating H3K4me3.

Disclosures: K. Alkhayer: None. **J. McDonough:** None. **E. Freeman:** None. **N. singhal:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.06/H9

Topic: B.13. Demyelinating Disorders

Support: National Multiple Sclerosis Society

Title: Cytokine responses to EAE are enhanced in Cx47KO as compared to Cx32KO and WT mice

Authors: *M. FREIDIN[1], E. GEORGIOU[2], K. A. KLEOPA[2], C. K. ABRAMS[1]
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Abstract: Oligodendrocytes express the connexins GJB2 (Cx32) and GJC2 (Cx47). Diseases such as Pelizaeus Merzbacher Like Disease (PMLD) due to mutations in Cx47 and CNS manifesting X-linked Charcot-Marie-Tooth disease (CMTX1CNS) due to mutations in Cx32 underscore the importance of oligodendrocyte connexins. Ongoing experiments in our lab are examining the hypothesis that loss of either oligodendrocyte connexins leads to increased susceptibility to Experimental Autoimmune Encephalomyelitis (EAE), a model for Multiple Sclerosis. Data from our laboratories show that mice lacking either Cx47 (47KO) or Cx32 (32KO) show increased susceptibility to EAE as evaluated by clinical rating scale; with 47KO mice more severely affected than 32KO mice. One explanation for the increased severity of EAE in 32KO and 47KO mice suggests that CNS immune responses are up-regulated with concomitant changes in the regulation of proinflammatory and anti-inflammatory cytokines. Mouse cytokine antibody arrays (RayBio® Mouse Cytokine Antibody Array 3) were used to examine expression of 62 cytokines in spinal cord samples from sham and MOG immunized WT, 32KO and 47KO mice at 7 and 12 days post injection (dpi). While IL6 and IL10 differed for both 47KO and 32KO in vehicle (CFA) controls (relative to WT control), 47KO showed changes in more cytokines following EAE than 32KO when compared to WT EAE; with significant changes in 10/62 and 23/62 of assayed cytokines at 7 and 12dpi, respectively. By contrast, no significant differences were observed in 32KO EAE at 7dpi and levels of only 3 cytokines were significantly altered at 12dpi relative to WT EAE. This correlates with the increased clinical severity observed in 47KO following EAE and suggests an enhanced proinflammatory response in mice lacking 47KO relative to 32KO and WT mice. These results also provide insights into potential pathways in exploring the roles of Cx47 and Cx32 in regulating oligodendroglial responses to inflammatory challenges.

Disclosures: M. Freidin: None. **E. Georgiou:** None. **K.A. Kleopa:** None. **C.K. Abrams:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.07/H10

Topic: B.13. Demyelinating Disorders

Title: Class iv semaphorin sema4a induces oligodendrocyte cell death and contributes to multiple sclerosis pathogenesis

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Abstract: Multiple Sclerosis (MS) is a progressive demyelinating disease of the central nervous system (CNS) whose causes are not yet well understood. It is thought to be caused by demyelination followed by a lack of or suboptimal re-myelination by oligodendrocytes in the CNS, however the extrinsic and intrinsic factors relating to oligodendrocyte death in MS are also not well understood. Identifying how alterations in oligodendrocyte biology contribute to MS pathogenesis is an essential prerequisite for developing better intervention strategies in MS treatment. We have previously shown a dose-dependent cytotoxic effect of the Class IV Semaphorin Sema4A on primary rodent oligodendrocytes. In rodents, Sema4A binds to Tim-2, a member of the T-cell immunoglobulin domain and mucin containing domain (Tim) family, a receptor that is expressed on activated T cells as well as oligodendrocytes. We recently discovered that Tim-2 is also the primary receptor for the iron delivery protein H-ferritin (Hft) and that oligodendrocytes are unique in the brain for taking up iron via this protein. However, the receptor for binding has yet to be identified in human oligodendrocytes as the gene for Tim-2 has not been detected in humans. We currently show that both recombinant Sema4A protein and Sema4A in the CSF of MS patients have a dose-dependent cytotoxic relationship with oligodendrocytes. Our data demonstrates that cell death following exposure to Sema4A is likely mediated via apoptosis. Our data also suggest that Sema4A levels in the CSF of MS patients could be used in combination with current standards of biomarkers for disease progression. Additionally, we have data that suggests addition of H-ferritin can prevent Sema4A cytotoxicity. Furthermore, we demonstrate that Tim-1 is the likely receptor that mediates Sema4A cytotoxicity in humans. Together, the data strongly suggest that utilizing H-ferritin against Sema4A will provide novel targeting for potential therapeutic treatments of demyelinating disorders.

Disclosures: B. Chiou: None. **E. Lucassen:** None. **J.R. Connor:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.08/DP03/H11 (Dynamic Poster)

Topic: B.13. Demyelinating Disorders

Support: NMSS Postdoctoral Grant FG 2092-A-1 to JOM

NMSS Center Grant CA 1064-A-4

Title: Remyelination of specific axonal domains in the somatosensory cortex

Authors: *J. L. ORTHMANN-MURPHY[1], C. CALL[2], E. G. HUGHES[3], P. A. CALABRESI[4], D. E. BERGLES[5]
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Abstract: Myelination in the cerebral cortex is sparse and often discontinuous along individual axons. It is not known if this pattern is stable over time or subject to constant remodeling. Defining the extent to which myelin is reorganized is essential to determine its role in experience-dependent plasticity within brain circuits. To determine if myelination is stable or subject to remodeling with age or experience, we performed long-term *in vivo* two photon imaging through a cranial window in adult *MOBP-EGFP* mice, which allowed visualization of oligodendrocytes and individual internode segments within the cortex. Our results indicate myelin internodes are highly stable**,** with the vast majority exhibiting little change in length over 50 days in 12-14 month-old mice. Changes in the overall pattern of myelination resulted primarily from oligodendrogenesis and incorporation of new internode segments, a process that was enhanced when mice were housed in an environment of enriched sensory experience. Cortical demyelination plays a critical role in the pathogenesis of progressive multiple sclerosis (MS), leading to physical and cognitive disability and brain atrophy. However, it is not known whether there are regional differences in myelin repair or whether the precise pattern of myelination is reconstituted after injury. To monitor the spatial and temporal dynamics of remyelination *in vivo*, 8-10 week-old mice were fed the oligodendrocyte toxin, cuprizone (0.2%), for three weeks and the resulting changes in myelination followed through longitudinal two photon imaging. Cuprizone exposure induced near complete oligodendrocyte loss and demyelination in the upper layers of the cortex within 5 weeks. Newly formed oligodendrocytes that appeared on or after the last day of cuprizone supplementation formed new internodes that, after an initial period of remodeling, remained stable for the duration of the imaging period (5 weeks of recovery). Oligodendrocyte cell bodies appeared in locations distinct from those occupied prior to cuprizone exposure; however, nodes of Ranvier and isolated internodes often appeared in a similar location, suggesting that some aspects of axonal specification that define permissive sites for myelination are maintained after demyelination. The ability to monitor remyelination of individual axons in living animals offers new opportunities for defining the mechanisms of oligodendrogenesis and axon recognition, as well as evaluate the effectiveness of potential therapeutics *in vivo*.

Disclosures: J.L. Orthmann-Murphy: None. **C. Call:** None. **E.G. Hughes:** None. **P.A. Calabresi:** None. **D.E. Bergles:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.09/H12

Topic: B.13. Demyelinating Disorders

Support: NICHD/NIH Grant R01HD067731

Title: Myelin in monkey and Down syndrome: Ballooned myelin is tethered at radial components and may reflect decreased conduction velocity and cognitive disabilities

Authors: *A. VAN HOEK[1], ***A. VAN HOEK**[1], A. RAMIREZ[2], M. SAUER[1], L. DAI[4], J. R. KORENBERG[3]
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Abstract: The conduction speed of an action potential is greatly enhanced by myelination and is significantly related to cognition, a fundamental issue in Down syndrome (DS). In DS, myelination development and repair are disturbed as are conduction properties indicated by fMRI. Reasoning that a 50% decrease in myelin thickness can slow conduction speed by 50%, we investigated the extent to which compacted myelin and radial components might be disturbed. Alterations are possibly related to the plethora of HSA chromosome 21 aneuploid genes (and MMU16 homologs). We generated immunocytochemical data for MBP, Olig 1, Olig 2, claudin 11 and GFAP by confocal microscopy, and determined the structure of myelin by electron microscopy in the Ts65Dn mouse, in the non-human primate macaca fascicularis and a brain kindly donated from a 76-year-old woman with DS. Immunocytochemistry of DS showed similar patterns of antibody labeling compared to the primate brain. However, EM results indicated a subset of axons with compact myelin, but in monkey and human a large proportion of highly ballooned myelin, and “onion” lamellated shapes thru the myelin layers, were observed that was most extreme in DS. Strong evidence of elegant helical arrangement of myelin structure was revealed by the pattern of ballooning, where the radial component was critical in tethering the balloons to prevent total disruption of myelin structure. All tissues had been fixed with 4%-paraformaldehyde (PA) (+0.2% glutaraldehyde (GA) for DS) in PBS and then post fixed/cross-linked with 2%-GA in 100 mM cacodylate). However, when calcium-acetate (100 mM) buffer was used instead of PBS in the primary fixative, ballooning was vastly decreased. It appears that in DS the myelin may be a significant focus of functional loss. We note the sensitivity of tissue preparation to Ca^{2+}, which may provide clues of axonal dysfunction. Ca^{2+} may be critical to opposing the negatively charged milieu, providing a physicochemical force to compact myelin. Overexpression of negative charged polysialic acids in the glycocalix of the oligodendrocyte has been shown to balloon myelin, while this was prevented by neuraminidase treatment. Recent results indicate consistent hypocalcemia in DS, the effects of which may be greatly augmented in the narrow extracellular plasma membrane regions of apposing myelin sheaths (high surface-to-volume ratios) where calcium concentration may reach the range used in our experiments. The results strongly suggest that myelin-neuronal interactions due to HAS 21 gene overexpression may play a critical role in intellectual disability, in normal aging and perhaps also in DS-AD.

Disclosures: **A. Van Hoek:** None. **A. Ramirez:** None. **M. Sauer:** None. **L. Dai:** None. **J.R. Korenberg:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.10/I1

Topic: B.13. Demyelinating Disorders

Support: ARISTEIA I "Myelin Tag" Project 593

ERC01 National Initiative grant

Hellenic Academy of Neuroimmunology Fellowship

Title: The synthetic microneurotrophin BNN27 protects mature oligodendrocytes against cuprizone-induced death through the NGF receptor TrkA

Authors: *D. KARAGOGEOS[1,2], G. BONETTO[3], I. CHARALAMPOPOULOS[4], A. G. GRAVANIS[5]
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Abstract: The neurosteroid Dehydroepiandrosterone (DHEA), a C19 adrenal steroid produced by neuronal and glial cells, binds with high affinity to all neurotrophin receptors (TrkA, TrkB, TrkC and $p75^{NTR}$), exerting strong neuroprotective effects. BNN27, a member of a chemical library of C17-spiroepoxy derivatives of DHEA lacking the endocrine effects of the parent molecule, has been shown to regulate neuronal survival through its selective interaction with NGF receptors (TrkA and $p75^{NTR}$), thus named *microneurotrophin*. However, its role on glial populations has not been evaluated. In this study, we investigated the potential protective effects of BNN27 in oligodendrocytes *in vitro* and *in vivo*.
We present evidence that BNN27 provides trophic, anti-apoptotic actions to mature oligodendrocytes, in a TrkA-dependent manner, when they are challenged with the copper chelator cuprizone (bis-cyclohexanone oxaldihydrazone) toxin in culture. We have used a specific TrkA inhibitor (10 nM) in oligodendrocyte cultures differentiated for 10 days, in the absence or the presence of cuprizone (100 μM), NGF (10 ng/ml) or BNN27 (100 nM). Cell death was subsequently evaluated revealing that BNN27 significantly reduced apoptosis of oligodendrocytes. Additionally, BNN27 treatment increased oligodendrocyte maturation as shown by branch complexity and MBP^+ membrane-like sheet formation. BNN27 also diminished LPS-induced microglia activation *in vitro*. The *in vivo* effects of BNN27 were investigated in the cuprizone mouse model of demyelination, an established model of CNS demyelination, characterized by the degeneration of mature oligodendrocytes. In this model that does not

directly involve the adaptive immune system, BNN27 preserved mature oligodendrocytes during demyelination, while reducing microgliosis and astrogliosis. Our findings suggest that BNN27 may serve as a lead molecule to develop neurotrophin-like, blood brain barrier permeable protective agents of oligodendrocyte populations and myelin, with potential applications in the treatment of demyelinating disorders.

Disclosures: D. Karagogeos: None. **G. Bonetto:** None. **I. Charalampopoulos:** None. **A.G. Gravanis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); co-founder of spin-off Bionature EA LTD, proprietary of compound BNN27 (patented with the WO 2008/ 1555 34 A2 number at the World Intellectual Property Organization).

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.11/I2

Topic: B.13. Demyelinating Disorders

Support: DMC Foundation 2015-1238

NMSS RG 4906A9

NIH, NINDS N5043783

NIH, NINDS N5067157

Title: Temporal association between molecular, electrophysiological, and behavioral changes in the OBiden mouse model of MS pathology

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Abstract: Multiple sclerosis (MS) is a neurodegenerative disease characterized by white and grey matter lesions contributing to a variety of disabling symptoms. The etiology of MS is generally considered to be immune-mediated; however, emerging research suggests that disease progression may involve additional pathogenic processes, including metabolic stress. Our *OBiden* (*OBi*) mouse model of MS-pathology focuses on adult-onset metabolic stress in oligodendrocytes as the etiology to parse any potential adaptive immune-mediated pathology. Using molecular, behavioral, electrophysiological and computer modeling analyses we have

compared *OBi* mouse pathology to that of MS patients to assess the pathophysiological relevance of this novel model to human disease. We have investigated molecular changes in hypothalamus, septum, hippocampus, entorhinal, and cingulate cortices to relate to behavioral changes such as stress, anxiety, sleep disturbances, memory loss, and depression which are commonly observed clinical symptoms in MS patients. To better understand the relationship between molecular and behavioral changes we have characterized behavioral endophenotypes in the mice which reveal memory deficits at 12-months and a depression-like endophenotype at 6- and 12-months. In addition, we find extensive hippocampal and cortical damage to neurons at 12-months in these mutants. We now focus on 5 time points (2, 6, 8, 10, and 12-months of age) to correlate molecular changes with the onset of two behavioral endophenotypes (memory loss and depression). We are using electroencephalography (EEG) to further investigate the hippocampal and cortical pathology in *OBi* mice, and observe reduced interhemispheric theta band coherence in 10- and 12-months but not at 6- or 8-months of age. Thus, our EEG findings correlate with memory changes in the *OBi* mice and suggest a shared cause - that of hippocampal pathology - which we are further analyzing using molecular, neurochemical, and transcriptomics approaches. Together, our current reveal a disease mechanism associated with oligodendrocyte metabolic stress comparable in several respects to MS. Thus, our novel model will likely provide insight into MS pathogenesis and provide new opportunities for the development of disease-modifying therapies for patients.

Disclosures: C.R. Richardson: None. **D.Z. Radecki:** None. **A. Gow:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.12/I3

Topic: B.13. Demyelinating Disorders

Support: ARSEP

Fondation pour la Recherche Médicale

Title: Effect of neuronal activity on remyelination

Authors: *C. HABERMACHER[1], F. C. ORTIZ[1], P.-Y. HOURY[1], M. GRACIARENA[2], B. NAIT-OUMESMAR[2], M.-C. ANGULO[1]
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Abstract: Oligodendrocytes precursor cells (OPCs) are the main source of remyelinating oligodendrocytes (OLs) in demyelinating diseases such as Multiple Sclerosis (MS). Although

remyelination can occur in MS lesions, it becomes increasingly incomplete and eventually fails with the progression of the disease. Recent reports in different animal models have shown that OLs preferentially myelinate electrically active axons in normal conditions. These findings suggest the interesting possibility that an increased activity of the demyelinated axons could modulate oligodendroglia dynamics to increase remyelination. The goal of the present study is to investigate whether an increased axonal activity *in vivo* modifies the dynamics of OPCs and OLs and promotes remyelination after acute demyelination induced in the adult mouse *corpus callosum* by focal injection of alpha-lysophosphatidylcholine (LPC). To increase the activity in LPC-demyelinating lesions, we use an optogenetic approach in Thy-1-ChR2-YFP transgenic mice. In these mice, the light-activated protein channelrhodopsin-2 (ChR2) is expressed in a subset of *corpus callosum* fibers and can be activated by blue light in freely moving mice after LPC-induced demyelination. To determine how neuronal activity in lesions affects OPC and OL dynamics as well as remyelination, we combined optogenetics with immunostainings, extracellular recordings and electron microscopy. We found that *in vivo* axonal photostimulation promotes remyelination. Our results shed light on the activity-dependent regulation of the remyelination process.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.13/I4

Topic: B.13. Demyelinating Disorders

Title: The Egr2-AS-RNA participates in transcriptional regulatory network following peropheral nerve injury

Authors: *M. MARTINEZ MORENO, C. GUETTA, N. TAPINOS
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Abstract: *Egr2* is a central regulator of Schwann cell myelination, and *Egr2* loss of function mutations have been associated with several types of human peripheral neuropathies. Following peripheral nerve injury, Egr2 expression is downregulated, resulting in initiation of demyelination. However, the role of epigenetic mechanisms, which regulate *Egr2* expression in the peripheral nervous system (PNS) during nerve injury response have not been established. We have previously described a long non-coding RNA antisense to the promoter of Egr2 (Egr2-AS-RNA) and its regulation after sciatic nerve injury. Here we describe that the expression of the Egr2-AS-RNA is regulated through Erk1/2 signaling to YY1. Dephosphorylation of Ser184 of YY1 after sciatic nerve injury regulates the direct binding of YY1 to the Egr2-AS-RNA. In

addition, the expression of the Egr2-AS-RNA is indirectly regulated by PP1α since increased expression of PP1α after sciatic nerve injury induces dephosphorylation of YY1. Finally, we present evidence for the role of c-Jun as part of a transcriptional regulatory network involving Egr2, YY1, PP1α and the Egr2-AS-RNA responsible for the generation of the denervated Schwann cell phenotype after nerve injury.

Disclosures: M. Martinez Moreno: None. **C. Guetta:** None. **N. Tapinos:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.14/I5

Topic: B.13. Demyelinating Disorders

Title: LPA receptors modulate oligodendrocyte differentiation and maturation

Authors: *K. I. LORRAIN[1], M. M. POON[2], B. STEARNS[3], J. BACCEI[3], A. BROADHEAD[4], A. DEARIE[4], A. GREENFIELD[5], J. R. CHAN[6], D. LORRAIN[4]
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Abstract: Lysophosphatidic acid (LPA) has been show to regulate numerous physiological functions, including cell proliferation and differentiation. In oligodendrocytes, LPA1 and LPA3 receptors are expressed and the expression pattern is correlated with oligodendrocyte differentiation. LPA signaling has been shown to have both pre and postnatal roles in the development of oligodendrocytes as well as potential regulators of myelination. In an effort to elucidate the specific roles of LPA1 and LPA3 on oligodendrocyte differentiation and maturation we used both gene KO animals as well as receptor selective small molecule antagonists. Oligodendrocyte precursor cells (OPCs) isolated from the mouse cortex were used to determine the effect of knocking out LPA1 and LPA3 receptors on basal differentiation. We show that LPA1 KO mice had higher OPC differentiation compared to heterozygous and WT controls. We also show that LPA3 KO mice had longer OPC processes lengths per cell compared to heterozygous and WT controls. Separately, LPA1 receptor selective and dual LPA1/3 receptor antagonists were shown to induce differentiation in wildtype animals. We further profiled these molecules in an organotypic brain slice assay confirming functional remyelination following lysolecithin damage. These data suggest that both receptor subtypes play key roles in oligodendrocyte differentiation and maturation.

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Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.15/I6

Topic: B.13. Demyelinating Disorders

Title: Mtmr2 loss increases mTOR signaling in Schwann cells

Authors: J. KIM[1], A. PATEL[1], A. ELIAS[1], F. L. ROBINSON[2], R. DOBROWOLSKI[1], *H. A. KIM[3]
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Abstract: Myotubularin-related protein 2 (Mtmr2), a phosphoinositide 3-phosphatase that dephosphorylates PI(3,5)P_2 and PI(3)P to generate PI(5)P and PI, respectively. Mutations in *MTMR2* gene cause Charcot-Marie-Tooth 4B1 (CMT4B1), a form of inherited peripheral neuropathy that affects myelin in the peripheral nervous system (PNS). Genetic conditional knockout mice for MTMR2 in Schwann cells recapitulate several aspects of CMT4B1, including reduced nerve conduction, loss of myelinated axons and myelin outfolding. A previous study has shown that MTMR2 loss results in accumulation of PI(3,5)P_2 in fibroblasts, indicating that the MTMR2-associated myelin abnormalities may be due to dysregulation of the biological function related to PI(3,5)P_2. PI(3,5)P_2 is found within the endo-lysosomal membrane, specifically within membranes of late endosomes and lysosomes. Therefore, it is possible that aberrant regulation of the endo-lysosome system may contribute to the myelin dysregulation in Schwann cells. To investigate the effects of MTMR2 loss in Schwann cells, generated Mtmr2 knockdown SCs using lentivirus-mediated shRNA transduction with 75-80% KD efficiency. In the Mtmr2 KD Schwann cells, we observed increased mTORC1 activity, which was accompanied by inhibition of the transcriptional activities of TFEB and ULK1. Inhibition of autophagic induction was also observed in the absence of Mtmr1. The effects of Mtmr2 KD on mTORC1, TFEB and ULK1 activities were reversed with a PIKfyve inhibitor, which reduces production of PI(3,5)P_2. Altogether, our data show that loss of Mtmr2 results in mis-regulation of the mTOR signaling and the down-stream transcriptional regulation of autophagy in Schwann cells

Disclosures: **J. Kim:** None. **A. Patel:** None. **A. Elias:** None. **F.L. Robinson:** None. **R. Dobrowolski:** None. **H.A. Kim:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.16/I7

Topic: B.13. Demyelinating Disorders

Support: NINDS

Charcot Marie Tooth Association

Title: Understanding the role of calcineurin in a mouse model of CMT1B neuropathy

Authors: C. REED, M. SIDOLI, M. L. FELTRI, *L. WRABETZ
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Abstract: Charcot Marie Tooth disease (CMT) is the most common inherited neuromuscular disorder. Mutations in *Myelin Protein Zero* (MPZ, P0) cause the dominant CMT1B demyelinating neuropathy. In the transgenic CMT1B-S63del mouse model, the folding of P0 is disrupted and causes a toxic gain of function. The accumulation of P0 in the endoplasmic reticulum (ER) leads to an unfolded protein response (UPR) and demyelination. The UPR sensor PERK kinase usually acts to relieve ER stress by phosphorylating eIF2alpha and attenuating protein translation. Surprisingly, Schwann cell-specific ablation of *Perk* in S63del mice, instead improves myelination, indicating a possible pathogenic role for PERK. Calcineurin, an important promyelinating signal, has recently been identified as a novel PERK substrate in other cell types. Here we present evidence for a physical interaction between PERK and calcineurin and increased calcineurin phosphatase activity in S63del nerves. Moreover, ablation of *calcineurin B* specifically in Schwann cells produces hypomyelination, which is synergistic with the hypomyelination of S63del nerves. These data suggest that calcineurin plays a role in the pathogenesis of CMT1B-S63del mice through an interaction with PERK.

Disclosures: C. Reed: None. **M. Sidoli:** None. **M.L. Feltri:** None. **L. Wrabetz:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.17/I8

Topic: B.13. Demyelinating Disorders

Support: NINDS (NIH) R01NS086818

Title: Monocarboxylate transporter (MCT1) in Schwann cells is a metabolic mediator of sensory axon myelination during aging

Authors: *M. K. JHA, K. RUSSELL, Y. LEE, A. HOKE, J. D. ROTHSTEIN, B. M. MORRISON
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Abstract: High metabolic demand and little reserve of energy stores necessitate the dependence of peripheral nerves on monocarboxylates, essentially lactate, as an energy source for proper functioning and maintenance. Monocarboxylate transporters (MCTs), as downstream mediators, govern cellular levels and functional consequences of monocarboxylates. MCTs transport lactate, pyruvate and ketone bodies that may be critical energy metabolites to axons. MCT1 is the predominant lactate transporter in the peripheral nerve and is expressed within Schwann cells (SCs) and perineurial glia. By employing MCT1 heterozygous null mice, we previously reported that nerve regeneration, in both sensory and motor axons, depends on MCT1 function. Recently, we produced and validated conditional MCT1 null mice that allow selective deletion of MCT1 from SCs. P0Cre::MCT1LoxP mice, which have selective knockdown of MCT1 in SCs, have normal development, both anatomy and electrophysiology; and are devoid of degeneration at early stage. As they age, P0Cre::MCT1LoxP mice developed hypomyelination and reduced conduction velocity in sensory, but not in motor, peripheral nerves, indicating that SC-specific MCT1 is critical for maintaining the myelination function of peripheral sensory nerves, and suggesting that metabolism in SCs myelinating sensory axons is different from those myelinating motor axons. Ongoing studies are determining the behavioral consequences of MCT1 deletion in SCs and the MCT1-dependent mechanisms of myelination in SC cultures. Taken together, our results not only illuminate the role of lactate and its transporter MCT1 in peripheral nerves during aging, but also suggest that they may be targets for the development of pharmacotherapies for demyelinating neuropathies.

Disclosures: M.K. Jha: None. **K. Russell:** None. **Y. Lee:** None. **A. Hoke:** None. **J.D. Rothstein:** None. **B.M. Morrison:** None.

Poster

125. Molecular and Cellular Mechanisms of Demyelination and Remyelination

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 125.18/I9

Topic: D.04. Somatosensation: Touch

Support: Intramural research program of the Eunice Kennedy Shriver NICHD, NIH

Title: PI4KA controls the levels of key lipids important for myelination in Schwann cells independently from the PI3K/Akt/mTOR pathway

Authors: *A. ALVAREZ-PRATS, Y. KIM, T. BALLA
Section on Mol. Signal Transduction. Program for Developmental Neurosci., Eunice Kennedy Shriver NICHD, NIH., Bethesda, MD

Abstract: Myelin is a key component of the nervous system essential for proper conductivity along the axons. In the peripheral nervous system (PNS), myelination is carried out by Schwann cells (SCs); and recently, we have identified phosphatidylinositol 4-kinase III-alpha (PI4KA), a lipid kinase, as a key regulator of myelination within the PNS using a mouse model which targeted PI4KA inactivation specifically in SCs. Here, we show that prolonged inhibition of PI4KA in cultured SCs, dramatically affects the amounts of phospholipids that are specifically important for myelin composition. Surprisingly, this inhibition did not affect the downstream PI3K/Akt/mTOR signaling axis, which is also required for proper myelination.

We used a potent and specific PI4KA inhibitor, A1, to inactivate the enzyme in a mouse SC line. Cells were treated with 100 nM A1 or DMSO for 24 h. To study the lipid profile of the cells after treatment we performed a lipidomic analysis, and to investigate if the PI3K/Akt/mTOR pathway had been affected, we stimulated the SCs with serum and followed the phosphorylation of Akt (both Ser473 and Thr308) and of the ribosomal p70 S6-kinase, a target of mTOR. We also followed the levels of the phosphoinositides PI4*P* and PI(4,5)P_2 by confocal microscopy using GFP-tagged lipid sensors (P4M of the SidM protein of *Legionella pneumophila* and the PLCd1-PH domain, respectively).

Consistent with our previous studies on sciatic nerves of mice, where PI4KA was genetically inactivated in SCs, our results showed that inhibition of this enzyme in cultured SCs caused a significant reduction of major components of the myelin sheath as phosphatidylserine (PS), phosphatidylethanolamine (PE), and sphingomyelin (SM). Interestingly, the phosphorylation of effectors of the PI3K/Akt/mTOR pathway after serum stimulation showed that PI 3-kinase activation was not significantly affected by the PI4KA inhibition in comparison to the control group. Likewise, 24 h treatment with the A1 inhibitor completely eliminated PI4P from the plasma membrane (PM); however, this treatment did not affect the PM localization of the PI(4,5)P_2 sensor PH domain.

In summary, these studies suggest that the primary mechanism by which PI4KA is important for myelination is not by maintaining PI(4,5)P_2 levels in the plasma membrane and supporting the PI3K/Akt/mTOR pathway. Instead, the enzyme is needed for the synthesis and distribution of selected major phospholipids that are basic lipid components of the myelin sheath. Current experiments are aimed at elucidating whether actin polymerization defects in PI4KA-inhibited SCs contribute to the myelination defects observed in the mouse studies.

Disclosures: A. Alvarez-Prats: None. **Y. Kim:** None. **T. Balla:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.01/I10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NNX14AI07G (CAL)

Title: Long-term, sex-specific effects of ^{56}Fe on cerebral A-beta and neuroinflammation in WT and Alzheimer's disease mice

Authors: *K. S. KOPACZ[1,2], B. LIU[3], K. X. LE[4], M.-A. PARK[5], S. WANG[5], A. BELANGER[5], S. DUBEY[5], P. HOLTON[5], V. REISER[6], W. TRIGG[7], M. DICARLI[5], C. A. LEMERE[8], B. LIU[2]
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Abstract: Background: Alzheimer's disease (AD) is the most common cause of dementia. Women have a higher lifetime risk of developing AD than men. Therefore, we hypothesized that young female AD mice would be more susceptible to long-term effects of space radiation on AD pathogenesis than age- and genotype-matched males.
Methods: Male and female 4 mo-old, APP/PS1dE9 Tg (AD) and WT littermate mice were exposed to whole body IRR with 1000 MeV/μ ^{56}Fe at 0, 10 or 50 cGy (n=13-18/group) at Brookhaven National Laboratory (Upton, NY). Longitudinal ^{18}F-GE180 TSPO PET imaging was performed on 4 mice/group (0, 50 cGy ^{56}Fe) 1 week before IRR and again 8 months post-IRR. Tracer uptake in whole brain, hippocampi, and thalamus (reference) was quantified using VivoQuant software. Radiation effects on brain Aβ (ELISA and IHC) and gliosis (IHC) were assessed at 12 months of age. Data was analyzed using ANOVA with a Bonferroni posthoc test.
Results: We observed an age- and AD-related increase in stable binding of the TSPO tracer (PET; 20-60 min post-injection) in both male and female AD mice from 4 to 12 months of age. To better distinguish the radiation effect vs. Aβ effects on brain inflammation, the ratio of post-IRR/pre-IRR PET tracer uptake was compared between non-IRR and 50 cGy ^{56}Fe IRR male and female AD mice. A significantly higher ratio of post-IRR/pre-IRR ^{18}F-GE180 uptake was observed only in IRR vs. non-IRR male AD mice, but not in female IRR vs. non-IRR AD mice, confirming that radiation had long-term, sex-specific effects on brain inflammation. Radiation (10 and 50 cGy ^{56}Fe) significantly increased insoluble cerebral Aβx-40 and Aβx-42 levels in male AD mice but had no effect in female AD mice. Also, 50 cGy ^{56}Fe IRR resulted in increased

Aβ plaque load and microgliosis (Iba-1 and CD68 staining) in male AD mice. In female AD mice, 10 cGy ^{56}Fe IRR increased GFAP astrocyte staining and 50 cGy ^{56}Fe IRR increased Iba-1 staining (but not CD68 staining), and had no effect on Aβ plaque load.
Conclusions: In summary, our data indicates that a single exposure of low-dose ^{56}Fe IRR resulted in long-term, sex-specific effects in response to deep space radiation by increasing cerebral Aβ and neuroinflammation in male AD mice but not females. These results correlate with our behavioral data from the same animals in which ^{56}Fe IRR resulted in genotype- and sex-specific late CNS radiation effects on locomotion, cognition, spatial learning, exploration, motor learning, and coordination. Further studies are warranted to determine if radiation-induced late CNS effects pose different risks for male and female astronauts on future deep space missions, such as the first manned mission to Mars.

Disclosures: K.S. Kopacz: None. **B. Liu:** None. **K.X. Le:** None. **M. Park:** None. **S. Wang:** None. **A. Belanger:** None. **S. Dubey:** None. **P. Holton:** None. **V. Reiser:** None. **W. Trigg:** None. **M. DiCarli:** None. **C.A. Lemere:** None. **B. Liu:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.02/J1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NASA Grant NNX14AI07G (CAL)

Title: Long-term, sex-specific neurobehavioural effects of ^{56}Fe radiation on WT and Alzheimer's disease mice

Authors: *G. G. LIU[1], B. LIU[1,2], P. J. LORELLO[3], P. A. MCKINNEY[3], B. CALDARONE[3,2], C. A. LEMERE[1,2]
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Abstract: As deep space travel becomes more feasible, the long-term risks of cosmic radiation must be determined, including the risk of accelerating brain aging and Alzheimer’s disease (AD). We examined sex-specific neurobehavioral responses to radiation in an AD mouse model by irradiating (IRR) 4 mo-old male and female APP/PS1dE9 Tg (AD) and WT littermates with 1000 MeV/μ ^{56}Fe ions at 0, 10 or 50 cGy (13-18 mice per sex/genotype/dose). Behavioral tests including SHIRPA (general health), Open Field (OF), Rotarod (RR), Grip Strength (GS), Y-Maze (YM), Elevated Plus Maze (EPM), Wire Hanging (WH), Tail Suspension (TS), Acoustic Startle (AS), Pre-Pulse Inhibition (PPI), and Contextual Fear Conditioning (CFC) were

conducted 7-8 months post-IRR (11-12 mos of age). Overall, ^{56}Fe IRR had no long-term effect on basic motor and sensory functions, grip strength, fatigue, startle, PPI, anxiety or depression. Significant 3-way interactions between gender, genotype and radiation dose were observed in the YM (total distance) and CFC (context test and total % freezing time). AD mice were more hyperactive in the OF test than WT mice, and motor activity (total distance) was further increased in 50 cGy ^{56}Fe IRR female AD mice. OF vertical counts (rearing activity) were significantly reduced in male AD mice IRR with 10 or 50 cGy ^{56}Fe, suggesting that radiation reduced exploratory behavior or possibly, induced escape behavior in male, but not female AD mice. In the Y Maze test, 10 and 50 cGy ^{56}Fe IRR male AD mice showed significantly less motor activity (total arm entries) and strong trends for impaired memory and exploration (reduced total alternations and % alternation) compared to control AD mice. Female AD mice showed no radiation effects in the YM test, suggesting that they were resistant to long-term cognitive effects of radiation. Female WT mice IRR with 50 cGy ^{56}Fe had significantly reduced total alternations but no change in % alternation. In the rotarod test, ^{56}Fe IRR led to improved motor coordination in female AD (50 cGy) and male AD (10 and 50 cGy) mice, and improved motor learning in male WT (50 cGy) mice, compared to relevant non-IRR controls. In the CFC test, ^{56}Fe IRR resulted in significantly reduced freezing times and total % freezing in the context test (Day 2) in male WT mice (50cGy), revealing radiation-induced memory deficits in male, but not female, WT mice. Our findings correlate with enhanced AD pathology in IRR male but not female AD mice. In summary, ^{56}Fe IRR resulted in a variety of genotype- and sex-specific late CNS radiation effects on locomotion, cognition, spatial learning, exploration, motor learning, and coordination.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.03/J2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Simmons SURPASs Award 2016 to AD

Title: Can curcumin protect retinal cells from nitric oxide-mediated cell death?

Authors: *D. GRAY[1], A. DENNIS[2]
[2]Biol., [1]Simmons Col., Boston, MA

Abstract: The mechanism of neuronal cell death in neurodegenerative diseases such as Alzheimer’s Disease (AD) and glaucoma is not yet completely understood. The main physical

characteristic of the disease includes the appearance of insoluble plaques and soluble aggregates containing a peptide called beta-amyloid (Ab). The plaques themselves may not be as toxic as smaller, soluble aggregates of Ab. These soluble aggregates may trigger a mechanism of cell death involving nitric oxide. This research perfected an *in vitro* model of cell death relevant to neurodegenerative disease using cultures of embryonic avian retinal neurons. Last year, transmitter release from isolated synaptic preparations derived from avian parasympathetic neurons displayed strong sensitivity to curcumin, reversing Ab induced inhibition of ACh release, implicating an antagonistic interaction with Ab and nitric oxide. The cell culture model was used to determine if curcumin, a known antioxidant that was recently proposed to slow the onset of Ab-associated pathology, can inhibit the rate of cell death in retinal cultures after nitric oxide exposure. We report that curcumin in micromolar concentrations is not able to significantly block or slow nitric oxide-mediated cell death in these retinal cultures. Future work will determine if curcumin can act on cell death directly-mediated by Ab in this model.

Disclosures: D. Gray: None. **A. Dennis:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.04/J3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Karolinska Institutet facility support

Denver University facility support

Title: Resolvin E1 reduces inflammation and enhances memory in the Ts65Dn mouse model of Down syndrome

Authors: *E. D. HAMLETT[1], E. HJORTH[2], A. LEDREUX[3], A. GRANHOLM[3], M. SCHULTZBERG[2]
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Abstract: Background: Alzheimer’s disease (AD) occurs early in individuals with Down syndrome (DS) and progresses to near uniformity by the age of sixty. Chronic inflammation, including microglia activation and elevated proinflammatory cytokines, are key hallmarks of DS-AD and novel therapeutics to limit this phenotype are needed. Inflammation is normally counter-regulated by specialized pro-resolving mediators (SPMs) which bind to a special class of conserved G-protein coupled receptors that promote resolution processes. In vivo SPM therapy is

in Phase II clinical trials but the therapeutic potential in chronic brain inflammation remains unexplored. Resolution factors in the DS brain are uncharacterized.
Objective: To reveal recent studies of the therapeutic potential of resolvin E1 (RvE1), a potent SPM, in the well characterized DS mouse model, Ts65Dn. To evaluate resolution components in postmortem brains from individuals with DS-AD.
Methods: At eight months of age, RvE1 or vehicle was delivered by subcutaneous mini-osmotic pumps for a 30-day period. At nine months of age, behavioral tasks were employed to assess locomotion, short-term vs. long-term object discrimination and cue-based spatial memory performance. We quantified SPM-related biosynthetic enzymes, resolution G-protein receptors, and microglia markers by immunohistochemistry. We quantified proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12) with multiplex ELISA in serum. We evaluated RvE1 receptors and signaling components by western blotting in specific brain region extracts.
Results: We observed high expression of resolution receptors in pathology-positive post mortem DS-AD brain sections. Chronic RvE1 treatment significantly enhances memory behavior tasks while normalizing open-field hyperactivity. Chronic RvE1 treatment reduces peripheral inflammatory cytokines and brain microglial activation in Ts65Dn mice.
Conclusions: Resolution receptor perturbations correlate with pathological events observed in postmortem brain tissue for those with DS-AD. Tour results suggest that there may be resolution dysfunction associated with chronic inflammation. The positive results from chronic RvE1 treatment in Ts65Dn mice suggest a potentially safe and transferable therapy that could target chronic inflammation by artificially enhancing the resolution.

Disclosures: E.D. Hamlett: None. **E. Hjorth:** None. **A. Ledreux:** None. **A. Granholm:** None. **M. Schultzberg:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.05/J4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Sarah Roush Memorial Fellowship, Indiana Alzheimer's Disease Center

NIH

Title: CX_3CR1 mediated microglial control of TREM2 macrophage responses in alzheimer's disease pathogenesis

Authors: *S. PUNTAMBEKAR[1], D. TUMBLESON-BRINK[2], A. OBLAK[3], G. E. LANDRETH[4], B. T. LAMB[5]
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Abstract: Little is currently known regarding the interactions among multiple immune cell types, namely the CNS resident microglia and blood derived monocytes/macrophages, in the development of region-specific pathological alterations in Alzheimer's Disease (AD). The neuronal chemokine CX_3CL1 has been implicated as a key mediator of neuroinflammation. Within the CNS, its cognate receptor, CX_3CR1 is expressed exclusively by microglia. Studies in APPPS1 mice have identified infiltrating, plaque-associated macrophages as the predominant $TREM2^{high}$ population in the CNS. TREM2 dependent compaction of Aβ plaques results in reduced neuronal dystrophy. While CX_3CR1 deficiency reduces cortical and hippocampal Aβ deposition, loss of TREM2 signaling in the APPPS1 model reduces amyloid pathology in the hippocampus with no significant effects in the cortex. These studies suggest that brain resident microglia (via CX_3CR1) and blood derived macrophages (via TREM2) play distinct roles in modulating region-specific pathology. Following detailed analysis of plaque distribution in APPPS1 mice, we have identified 4 anatomical regions of interest, namely the cortex, hippocampus, thalamus and medulla. While $6e10^+$ plaques are significantly reduced in the cortex and hippocampus, their numbers are unaltered in the thalamus and are significantly higher in the medulla of 4 month old APPPS1;*Cx3cr1*$^{-/-}$ mice. However, CX_3CR1 deficiency increases the proportion of $ThioflavinS^{dim}$ plaques in all 4 regions of interest, indicating an overall deficit in plaque compaction. Histological analysis of neuronal dystrophy, a hallmark of AD, shows that $AT8^+$, $AT180^+$ and $LAMP1^+$ neurites are reduced in the cortex, hippocampus and thalamus but are increased in the medulla of APPPS1;*Cx3cr1*$^{-/-}$ animals. We hypothesize that CX_3CR1 signaling regulates AD pathology by a) controlling early microglial activation/phagocytosis during disease initiation, b) modulating microglial activation and plaque associated microglial barriers, thereby regulating toxic Aβ deposition, and c) regulating CCL2-mediated influx of $TREM2^{high}$ macrophages, which in-turn mediate plaque compaction and reduce neurotoxicity. Since microglial activation is the earliest response to onset of pathological changes, we propose that modulating early, microglial activation can shape subsequent AD pathology and $TREM2^+$ peripheral macrophage responses.

Disclosures: S. Puntambekar: None. **D. Tumbleson-Brink:** None. **A. Oblak:** None. **G.E. Landreth:** None. **B.T. Lamb:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.06/J5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: KAKENHI 16K19776

Title: Mesenchymal stem cell-conditioned medium induces microglia into M2a phenotype and promotes amyloid beta-phagocytosis

Authors: *N. IWAHARA
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Abstract: Background Accumulation of amyloid β (Aβ) is a prominent pathological feature in Alzheimer's disease (AD). Promoting a clearance of Aβ is considered to be an effective therapeutic strategy. Transplantation of mesenchymeal stem cells (MSC) has shown to reduce Aβ plaques in AD mouse models, however, its therapeutic mechanisms were not fully understood. Objective The purpose of this study is to examine the effects of MSC-conditioned medium (MSC-CM) on microglial Aβ-clearance. Patients and Methods / Material and Methods The method of bone marrow derived MSC culture was based on Honmou's method (*Brain Res. 2006*;*1123:27-33.*). MG6 cells, mouse microglial cell line (*Biochim Biophys Acta 2005*;*1726:177-186*), were cultured with MSC-CM. After the MSC-CM-treatment, mRNA levels of M1 and M2 makers were measured by qRT-PCR. Lipopolysaccharide (LPS) was added for evaluating pro-inflammatory cytokines-productivity, and quantities of pro-inflammatory cytokines were measured by ELISA. MG6 cells were cultured with fluorescently-labeled Aβ1-42 and intensity of intracellular fluorescence was measured by FACS. Results Treatment of MSC-CM increased the mRNA levels of M2 makers (Arginase1 and CD206) and reduced that of the M1 makers (TNFα and IL6). Additionally, it also induced functional change from M1 to M2. Productivity of pro-inflammatory cytokines (TNFα and IL6) was suppressed by MSC-CM-treatment. And it increased the amount of intracellular Aβ. Conclusion We show that MSC-CM induced microglia into M2 phenotype and promoted its Aβ-phagocytosis. MSC secrete various humoral factors such as cytokines and exosomes. Furthermore, MSC-CM possibly contains other unknown factors. To clarify the mechanism that underlies the effects of MSC-CM, further studies are needed.

Disclosures: N. Iwahara: None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.07/J6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R00 AG044445

NIH Grant P30 AG028383

Title: The association of rod shaped microglia with aging and neurodegenerative disease

Authors: *A. D. BACHSTETTER[1], E. T. IGHODARO[2], E. L. ABNER[2], P. T. NELSON[2]
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Abstract: A subtype of microglia is defined by the morphological appearance of the cells as “rod-shaped”. Little is known about this intriguing cell type, as there are only a few case reports describing rod-shaped microglia in the neuropathological literature. The presence or absence of rod-shaped microglia was scored on IBA1 immunohistochemically stained slides for the human hippocampus. Rod-shaped microglia were found to account for a substantial proportion of the microglia cells in the hippocampus of both demented and cognitively intact aged individuals (total n=39 cases). We hypothesized that aging could be a defining feature in the occurrence of rod-shaped microglia. To test this hypothesis, two independent series of autopsy cases (total n=168 cases), which covered the adult lifespan from 20 - 100+ years old, were included in the study. The results demonstrated that aging, rather than Alzheimer’s disease or traumatic brain injury, is more strongly associated with the presence of rod-shaped microglial cells in the human brain.

Disclosures: A.D. Bachstetter: None. **E.T. Ighodaro:** None. **E.L. Abner:** None. **P.T. Nelson:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.08/J7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Saban Family Foundation

Maurice Marciano Family Foundation

Title: Immunomodulation: The path to brain homeostasis in old late-stage Alzheimer's mouse models

Authors: *J. DOUSTAR[1], *J. DOUSTAR[1], T. TORBATI[1,5], D.-T. FUCHS[1], Y. KORONYO[1], J. SHEYN[1], A. RENTSENDORJ[1], P. K. SHAH[2,3,4], K. L. BLACK[1], S. LI[6], M. KORONYO-HAMAOUI[1,2]
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Abstract: Background. Previously, we have shown that immunomodulation with glatiramer acetate (GA) in adult (10-13 month old) mouse models of Alzheimer's disease (AD) leads to alleviation of neuropathology and preservation of synapses and cognitive function. The therapeutic effects were attributed to increased cerebral recruitment of monocytes responsible for amyloid-beta (Aβ) clearance and regulation of neuroinflammation. However, it has been argued that adult AD mouse models merely correspond to the pre-clinical human disease, presenting limited aspects of aging-related processes linked to AD. Here, we explored the impact of GA immunization on old, late-stage double-transgenic $APP_{swe}/PS1_{\Delta E9}$ mice (ADtg; 21-24 month old). This particularly old mouse cohort is more comparable with clinical stages of the human disease and may provide insight into the translational potential of such AD therapy. **Method.** Experiments included twenty-month-old ADtg mice, receiving weekly subcutaneous injections of either GA or PBS for 8 weeks, and age-matched naïve wild-type littermates (n=7 mice per group). Brain tissues were analyzed for soluble and insoluble Aβ levels, inflammatory biomarkers, and synaptic integrity. **Results.** In comparison to PBS-treated controls, mice immunized with GA displayed significantly decreased hippocampal and cortical $GFAP^+$ reactive astrogliosis. In spite of abundant cerebral Aβ plaque burden at this late-stage disease with no apparent effect on Aβ burden, there was a remarkable reduction in the number of $GFAP^+$ astrocytes per Aβ plaque in GA-immunized vs. PBS control mice. In-depth analysis of astrocyte morphology and functional biomarkers showed highly reactive astrocytes and increased expression of glutamine synthetase (GS), an astrocyte-associated enzyme involved in degradation of extracellular synaptic glutamate, in ADtg mice. GA immunization restored astrocyte phenotype and homeostatic GS levels, comparable with levels measured in WT mice. This effect was shown in total GS expression, GS^+ cell number, and GS expression per astrocyte. Given that synaptic loss is tightly associated with cognitive decline, we analyzed synaptic density in these aged mice and found enhanced presynaptic VGluT1 and postsynaptic PSD95 biomarker expression following GA immunization. **Conclusion.** This study demonstrates the neuroprotective effects of GA immunomodulation in old late-stage ADtg mice. Although cerebral Aβ burden has reached a plateau in these mice, we observed notable benefits in inflammatory response, glial cell phenotypes, and synaptic preservation. This study provides the foundation to translate GA treatment to humans.

Disclosures: J. Doustar: None. **T. Torbati:** None. **D. Fuchs:** None. **Y. Koronyo:** None. **J. Sheyn:** None. **A. Rentsendorj:** None. **P.K. Shah:** None. **K.L. Black:** None. **S. Li:** None. **M. Koronyo-Hamaoui:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Program#/Poster#: 126.09/J8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The BrightFocus Foundation (formerly the AHAF)

The Coins for Alzheimer's Research Trust (C.A.R.T) Fund

Saban Family Foundation

Maurice Marciano Family Foundation

The National Center for Advancing Translational Sciences through CTSI Grant UL1TR000124

Title: Potency of ACE-overexpressing macrophages to resist Alzheimer's disease pathology

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Abstract: We previously introduced targeted overexpression of angiotensin-converting enzyme (ACE) to $CD115^+$ myelomonocytic cells (ACE10 model) in the double-transgenic $APP_{SWE}/PS1_{\Delta E9}$ murine models of Alzheimer's disease (AD^+ mice). ACE was shown to degrade neurotoxic $A\beta_{1\text{-}42}$, a peptide that is tightly associated with AD. AD^+ACE10 mice exhibited minimal to almost no AD-like pathology and had striking preservation of cognitive functions. These benefits were dependent on the catalytic activity of ACE and were lost when ACE was pharmacologically blocked with ramipril. AD^+ACE10 mice had reduced neuroinflammation (microgliosis and astrogliosis), yet increased recruitment of peripheral monocytes and macrophages (Mo/MΦ) involved in Aβ-plaque clearance. Here, we explored the immune mechanisms by which ACE10 alters the immune profile of Mo/MΦ and enhances their ability to resist AD-associated pathology. We measured the impact of bone-marrow (BM) transplantation and adoptive transfer of ACE10-Mo on Mo infiltration to the brain, as well as neuropathology and cognitive outcomes in AD^+ mice. The acquired Mo/MΦ phenotype was evaluated both in vivo and in vitro; the latter was in BM-derived primary MΦ cultures in response to purified populations of fibrillar and non-fibrillar $A\beta_{1\text{-}42}$ assemblies. Our in vivo studies demonstrated that adoptive transfer of $CD115^+$ACE10-Mo into peripheral blood of symptomatic AD^+ mice resulted in retained cognitive function (Barnes maze test) and attenuation of neuropathology compared to AD^+ mice receiving adoptive transfer of WT-Mo or PBS injection. BM transplantation studies suggested increased presence of infiltrating ACE10-MΦ surrounding cerebral Aβ plaques with reduced TNFα secretion relative to WT-MΦ. Importantly, our in vitro studies using ACE inhibitors indicated that enhanced phagocytic activity depend on ACE catalytic activity. Binding and engulfment of fibrillar, protofibrillar, and oligomeric $A\beta_{1\text{-}42}$ was increased in ACE10-MΦ vs. WT-MΦ, with elevated expression of surface scavenger receptors (CD36, Scara-1, TREM-2, CD163). Following exposure to $A\beta_{1\text{-}42}$ assemblies, extracellular degradation of $A\beta_{1\text{-}42}$ and cell survival was increased in ACE10-MΦ. ACE10-MΦ also exhibited an anti-inflammatory cytokine

profile and a 2.5-fold elongation of cell processes relative to WT-MΦ, suggesting enhanced polarization towards a pro-healing phenotype. These studies provide in vivo and in vitro evidence to support a potential therapeutic role for ACE-overexpressing Mo/MΦ in resisting neurotoxic Aβ-induced inflammation in murine AD models.

Disclosures: **Y. Koronyo:** None. **A. Rentsendorj:** None. **J. Sheyn:** None. **D. Fuchs:** None. **E.Y. Hayden:** None. **S. Li:** None. **K.L. Black:** None. **K.E. Bernstein:** None. **D.B. Teplow:** None. **S. Fuchs:** None. **M. Koronyo-Hamaoui:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.10/J9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NRF-2015R1C1A2A01054270

Title: Amyloid beta vaccination in conjunction with bvPLA2 ameliorates Alzheimer's disease patholgoy in murin model

Authors: ***H. BAE**, H. BAEK, N. KIM, C. LEE
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Abstract: Alzheimer's disease (AD) is the most common form of dementia and characterized by an imbalance between the production and clearance of amyloid-beta and tau protein. Vaccination against amyloid-beta peptide results in dramatic reduction of amyloid-beta pathology in experimental mouse models. Our recent study demonstrated that bvPLA2, the major component of BV, causes immune tolerance by increasing the population of CD4+CD25+Foxp3+ Tregs in cisplatin-induced nephrotoxicity, allergic asthma and Parkinson's disease murine model. Here, we invetigated that the effect of bvPLA2 to induce antigen-specific Tregs to ameliorate AD pathology through linked immunosuppression. First, we investigated whether bvPLA2 would improve the cognitive function and the pathological features of AD in amyloid-beta-vaccinated 3xTg-AD mice. bvPLA2 treatment dramatically ameliorated learning and memory deficits in amyloid-beta-vaccinated AD mice. In addition, bvPLA2 significantly reduced Amyloid-beta deposits in the hippocampus and cortex region of AD mice, compared with the amyloid-beta vaccinatated AD mice group. Next, we systemically administered antigen-specific Treg populations generated in the absence or presence of bvPLA2 into 3xTg-AD mice. Systemic transplantation of amyloid-beta specific Tregs into 3xTg-AD mice improved cognitive functiond and reduced depostiion of amyloid-beta plqaues. Furthermore, adoptive transfer of Tregs generated in the presence of bvPLA2 showed reduced amyloid-beta plaques and diminished learning and memory ability compared with Tregs prepared in the absence of bvPLA2. This

opens the possibility of new therapeutic strategy to target Treg to tissue-specific antigens for the treatment of AD.

Disclosures: **H. Bae:** None. **H. Baek:** None. **N. Kim:** None. **C. Lee:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Program#/Poster#: 126.11/J10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Identification of Enterococcus Faecalis in the human Alzheimer's brain

Authors: *Z. BOWERS[1], T. SIVY[2], M.-S. SONG[4], N. KOLLI[5], P. MAITI[7], G. L. DUNBAR[6], C. L. WEAVER[3]
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Abstract: Alzheimer's disease (AD) is a critical public health issue. AD is a degenerative brain disease and the most common cause of dementia (Korolev, 2014). Although research has revealed a great deal about Alzheimer's, much remains to be discovered about the biological changes that cause Alzheimer's. Interestingly, the role of chronic infection in AD pathology has been receiving attention for the past thirty years. For example, it has been shown that β-amyloid might function as an antimicrobial peptide reacting to pathogen entry into the central nervous system (Soscia, 2010; 2016). One suggested link between infection and AD is edentulism, the complete loss of teeth. Edentulism can result from chronic periodontal disease due to infection by Enterococcus faecalis (E. faecalis) (Gallo, 2005). Edentulism has been shown to be present in 46% of individuals with AD (Gallo, 2005). Studies have demonstrated that E. faecalis can migrate within the human body and even enter the CNS ((Submuth, 2000; Mylona, 2012). When cortical cells grown in-vitro are introduced to E. faecalis, posttranslational modifications to the tau protein can are produced that are similar to those seen in Alzheimer brains (Underly, 2015). The purpose of this study was to determine if the presence of (E. faecalis) a gram-positive bacterium, existed within human Alzheimer tissue. Two methods were used to identify the presence of infection. The primary method was polymerase chain reaction (PCR) analysis utilizing DNA extracted from whole tissue samples. Amplification and electrophoresis was conducted using methods outlined in Dutka-Malen S, Evers S, Courvalin P., 1995. Eight samples were utilized, six with AD and six age-matched control. In addition to the eight samples, two positive controls were analyzed; one containing E. faecalis plasmid grown in culture and a

second containing an external plasmid. The second method involved immunohistochemistry using 5 µm paraffin-embedded sections. The primary antibody used was an anti-Enterococcus rabbit polyclonal antibody (Abcam ab19980). The first two trials were reacted with 3,3′-Diaminobenzidine (DAB), while the second set of trials utilized a fluorescent secondary, Alexa Fluor 488 goat anti-rabbit IgG(H+L). This study was conducted in attempt to help further describe the variety of infectious agents that may generate a number of deleterious conditions contributing to AD.

Disclosures: Z. Bowers: None. **T. Sivy:** None. **M. Song:** None. **N. Kolli:** None. **P. Maiti:** None. **G.L. Dunbar:** None. **C.L. Weaver:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NHRI&CGST106-1901-01-10-02

Title: Treatments of the anti-diabetic drugs promotes microglial Aβ phagocytosis

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Abstract: Increasing evidence is emerging that diabetes mellitus (DM) can be an early non-genetic risk factor in the pathogenesis of Alzheimer's disease (AD) and AD is a type III DM due to the findings of insulin resistance and DM-associated metabolic stresses in AD patients. Previously, we have shown that a high-fat diet and low-dose injection of streptozotocin (HFSTZ)-induced diabetic conditions in APP/PS1 mice exacerbated pathological features of AD and contributed to vascular inflammation, abnormal cerebral glucose metabolism, and metabolic stresses in the periphery. Recently, some anti-diabetic drugs have been reported to exert anti-inflammatory effects and can be neuroprotective. It is conceivable to postulate that counteracting DM by pharmacological means using anti-diabetic drugs may ameliorate the early development of the pathological features in AD. However, the role of the anti-diabetic drugs in the modulation of phagocytic activity toward Aβ in microglia remain unknown. In the present study, we demonstrate that treatments of sitagliptin, a selective dipeptidyl peptidase 4 (DPP-4) inhibitor, enhanced Aβ phagocytosis in LPS-activated microglia. Similarly, exendin-4, a long-acting glucagon-like peptide-1 (GLP-1) analogue, also increased microglial Aβ phagocytosis and co-treatments of exendin-4 with sitagliptin showed additive effects at a dose-dependent manner on enhancing Aβ phagocytosis. These data suggest that GLP-1 may function to promote Aβ

phagocytosis in microglia. Furthermore, our data indicate that the effects of these anti-diabetic drugs on microglial Aβ phagocytosis are positively associated with the gene upregulation of the receptors involved in Aβ cascade, but not with the expressions of pro-inflammatory indications. Our data suggest that sitagliptin and exendin-4 could facilitate Aβ phagocytosis at least in part through modulating transcription levels in microglia. Taken together, these data demonstrate for the first time that treatments of these anti-diabetic drugs may instigate the GLP-1-mediated Aβ phagocytic activity in microglia, which can be beneficial for AD therapy.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Program#/Poster#: 126.13/J12

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR Grant PJT-149031

Title: Systemic autoimmunity: A sex-specific factor in Alzheimer's-like disease

Authors: M. KAPADIA[1], F. MIAN[2], D. MA[3], E. ROSA[1], B. MICHALSKI[1], P. FORSYTHE[2], B. SAKIC[1], *M. FAHNESTOCK[1]
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Abstract: Introduction: The 3xTg-AD mouse is a well-established animal model of Alzheimer's disease (AD). However, we recently reported that 3xTg-AD males no longer exhibit AD-like plaque/tangle pathology at 1 year of age. Yet, they exhibit anxiety-like behaviour and learning/memory deficits and also manifest signs of systemic autoimmunity within the first 6 months of life. In contrast, 1-year-old female 3xTg-AD mice reportedly show severe plaque/tangle pathology. This study was designed to compare immune status in both sexes and to determine whether systemic autoimmunity is damaging or neuroprotective. **Methods**: 3xTg-AD and non-transgenic mice of both sexes were administered the immunosuppressant cyclophosphamide 2 days/week in sucrose-laced water from 4 weeks to 6 months of age. Mice underwent testing in a behavioral battery and were euthanized for post-mortem assessment of immune status and molecular markers of prodromal AD-like pathology and learning/memory. **Results**: Chronic immunosuppression abolished autoimmune manifestations and reduced soluble Aβ levels in 3xTg-AD mice, but failed to normalize low brain mass, brain-derived neurotrophic factor expression or spatial learning capacity. More interestingly, it worsened performance in anxiety-related tasks and accelerated fur graying, producing distinct patterns of discoloration between the sexes. Signs of systemic autoimmunity (e.g., splenomegaly, low hematocrit and

increased anti-dsDNA autoantibody levels) were more profound in untreated 3xTg-AD males than females, suggesting sex is an important factor in determining the magnitude of immunological perturbations. **Conclusions**: The current study reveals that 3xTg-AD mice develop an early autoimmune response that is more profound in males than in females. This sex-dependent autoimmunity is associated with increased Aβ load and reduced anxiety-related behaviors in 3xTg-AD mice. Consistent with evidence implicating the immune system in AD etiology, our results point to a complex role for genetics and autoimmunity in modulating brain and body physiology in an end-point dependent manner. These findings suggest that systemic immune manifestations influence AD pathogenesis and may shed light on the increased prevalence of AD in females.

Disclosures: M. Kapadia: None. **F. Mian:** None. **D. Ma:** A. Employment/Salary (full or part-time):; Euroimmun Medical Diagnostics Canada Inc.. **E. Rosa:** None. **B. Michalski:** None. **P. Forsythe:** None. **B. Sakic:** None. **M. Fahnestock:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Strategic Priority Research Program of the Chinese Academy of Sciences (XDB02020002)

Title: Early changes in hippocampus gliovascular unit and spatial memory in different aging APP/PS1 transgenic mouse model for Alzheimer's disease

Authors: *N. WANG, R. MAO, L. XU
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Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by cognition impairment and two histological hallmarks: beta-amyloid (Aβ) plaques and neurofibrillary tangles in the brain. About 35million people worldwide are affected by this progressive cognitive decline .More and more researchers reveal it's pathogenesis involve in multiple concomitant factors.AD is an age related disease, however, the early phases of AD have received relatively less attention, so studying early phases of AD is important for early detection and treatment . The neurovascular unit (NVU) comprises neurons, vascular cells and glial cells, which are important for brain homeostasis and function. A mouse model of AD overexpressed the delta exon 9 variant of presenilin1 (PS1; also known as PSEN1), in combination with the Swedish mutation of β amyloid precursor (APP) and littermate controls at 3,4,7 and 9 months were used. Spatial memory were tested by Morris water maze. After test, mice were anesthetized

and transcardially perfused with PBS followed by 4% paraformaldehyde. OCT-embedded frozen brain tissue was cryosectioned at a thickness of 30μm for immunofluorescence. In Morris Water maze test, At 3 months, APP/PS1 mice performed similarly with WT mice. The learning ability of 4 months APP/PS1 mice was slight impaired, but short term memory was normal. At 7 months and 9 months AD mice exhibited seriously spatial memory defect. However, the Aβ plaque depositions were detected at 7 months. At 7 months the microglia and astrocyte became active and aggregated. Glia cells respond to and surround plaques, degrading Aβ by phagocytosis. However, chronic activation of these cells shift microglia to a more proinflammatory and less phagocytic state. The microvessel density exhibited significant reduction from the seventh month and vascular amyloidosis also were found. Our studies show that the hippocampus neurovascular unit are changed and impaired early at 7 months, Aβ plaque may contribute to this defect. The neurovascular unit play an important role for brain activity, their defect may induce the neuron activity abnormally, which then may induced the spatial memory defect.

Disclosures: **N. Wang:** None. **R. Mao:** None. **L. Xu:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.15/K2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: TCVGH-HK1048009

Title: The effects of lipopolysaccharide-induced TNF-α and NO production following alcohol exposure in rat mixed glial cultures

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Abstract: Alcohol (EtOH) is considered to be one of the most commomly abused chemical. Alcohol consumption has various effects on various organs. Experimental evidence indicated that alcohol consumption can alter the inflammatory response. Furthermore, neuroinflammation is thought to be a factor in alcohol-induced neurodegeneration, and microglia activation may be a key role. It is known that ethanol exposure induced the microglial abnormal activation to release TNF-α and nitric oxide (NO) and decreased the number of neurons in mice brain. However, some data indicated that the microglial activation was not equivalent to neuroinflammation in EtOH-induced neurodegeneration. Alzheimer's disease (AD) is the most common neurodegenerative disorder. It is associated with neuroinflammatory response, too. Glial cells

(including astrocytes and microglial cells) in the brain that promote brain inflammation in response to stimuli. The processes accompany with inflammatory response are increasing in the expression of transcription factor NFκB, inducible NO synthase (iNOS) and the release of mediators (ex. NO and cytokines). Ultimately, these events may create a vicious cycle to induce neuronal injury. Even though glial cells are very important constituents in the brain, but the investigation of effects of EtOH on glia are not clear. We want to know the role of glial cells in neurodegeneration following alcohol exposure. In this study, we estimated the influence of alcohol on lipopolysaccharide (LPS)-induced neuroinflammation in mixed glial cells. The *in vitro* experiment: rat cortical mixed glial cultures will be subjected to (1) control; (2) LPS treated with 1, 10, 100, 500 or 1000 ng/ml; (3) Alcohol treated with 0.1, 0.5, 1 or 2 % ; (4) pretreatment of alcohol following LPS treatment; all of above were treated for 1, 3 or 5 days. Cell density and morphology will be observed by phase-contrast microscopy. Cell injury will be assessed by MTT reduction. The production of TNF-α and NO will be measured to estimate the inflammatory responses. Our *in vivo* data showed that the neuron number was decreased significantly in prefrontal cortex and hippocampus (CA1). The *in vitro* data indicated that the cell viability significantly decreased in LPS treatment for 1 day, but the MTT reduction (% of control) was about 90 %. The production of TNF-α and nitrite was significantly increasing in 1, 3 or 5 days. MTT reduction and TNF-α or NO production in alcohol exposure was not significant change. Pretreatment with alcohol in high doses (1 % and 2 %) significantly decreased the LPS-induced TNF-α and NO production. We suggested that alcohol can attenuate the LPS-induced inflammatory response

Disclosures: **J. Wang:** None. **C. Cnen:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01-NS092865

R03-NS090214

P50-AG05681

RO1NS075321

Title: Chronic neuroinflammation and demyelination in alzheimer disease and parkinson disease

Authors: F. HAN[1], N. J. CAIRNS[2], J. S. PERLMUTTER[3], *J. XU[1]
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Abstract: Microglia and astrocytes play important roles in mediating the immune processing of central nervous system (CNS). Substantial evidence suggests that microgliosis and astrocytosis directly are both features of the two most common neurodegenerative diseases: Alzheimer disease (AD) and Parkinson disease (PD). Chronic neuroinflammation, the sustained activation of microglia and astrocytes, may contribute to accelerated AD or PD disease progression. Recent studies indicate astrogliosis may inhibit remyelination in demyelinating disorders such as multiple sclerosis. In this study, we investigated the relationship between neuroinflammation and neurodegeneration in postmortem human brain tissue (n=15 including 6 AD, 5 PD and 4 age-matched, cognitively normal controls (NC)). We conducted systematic and quantitative immunohistochemistry (IHC) to examine neuroinflammation using GFAP antibody, a marker for astrocytes and Iba1 antibody, a marker for microglia. Neurodegeneration in white matter was evaluated by myelin and axon staining in adjacent brain tissue sections. Eight of 15 cases (4 AD, 3 PD and 1 NC) have extensively activated microglia and astrocytes in the striatal white matter. Quantitative analysis of IHC in these 8 cases showed a significant negative correlation between GFAP (but not Iba-1) and myelin (but not axon) staining in white matter ($r^2 = 0.78$, $p < 0.005$). These observations indicate that astrocytosis in white matter may contribute to demyelination in AD, PD and normal aging. In contrast, expression of GFAP (but not Iba-1) had a strong nonlinear correlation with myelin (but not axon) density in the 7 cases with very low GFAP staining, suggesting that resting astrocytes in the white matter may contribute to myelination.
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Key words: Neuroinflammation; astrogliosis, myelination.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Program#/Poster#: 126.17/K4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Similar patterns of altered innate immunity and hematopoietic cell recruitment develop in Aβ-depositing (APP/PS1) and tauopathy (Tg4510) transgenic models of Alzheimer pathology

Authors: *R. B. NELSON[1], I. KADIU[2], L. K. ISAAC[3], M. J. DENBLEYKER[4], S. KRZYZANOWSKI[5], N. BREYSSE[6], J. A. TAMM[7], A. ABDOURAHMAN[8], P. D. WES[9], P.

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Abstract: Genome-wide association and expression studies indicate a causal role for the innate immune system in AD. Ultrastructural evidence from AD brain indicates that hematopoietic cell infiltration is one manifestation of this immune system dysfunction, but little is known about the identity of these recruited cells or factors influencing their recruitment. Using genome-wide expression pathway analysis, we found that the "dendritic cell maturation" pathway was the most highly upregulated of >400 canonical pathways in both APP/PS1 Abeta-depositing mice and Tg4510 tauopathy mice by 6 and 8 mos of age, respectively. The "leukocyte extravasation pathway" was the 4th and 8th most highly upregulated pathway in Tg4510 and APP/PS1 mice, respectively. Together, these data suggested that recruitment of dendritic cells might be occurring in both models. We selected the dendritic cell-enriched marker CD11c as a probe to explore this hypothesis since *Itgax,* the gene coding for CD11c, showed the greatest increase in expression of all genes in either model. The CD11c mAb N418 revealed an increasing density of CD11c+ cells in the brain of each disease model with age. CD11c+ cells were preferentially clustered around neuritic plaques in APP/PS1 mice, while CD11c+ cells had a broader, more uniform parenchymal distribution in Tg4510 brain. We investigated the origin of these CD11c+ cells by labeling circulating cells in blood with the membrane tag DiO, and examining brain for infiltrating DiO+/CD11c+ cells 48 hr later. We found a robust signal of recruited CD11c+ cells in both APP/PS1 and Tg4510 mice, but virtually no recruitment in corresponding WT control mice. This recruitment was selective for CD11c+ cells in that we did not detect infiltration of DiO+/CD11c- cell populations in brain. Together these data indicate that a population of CD11c+ cells, likely representing a type of dendritic cell, are selectively recruited from blood into brain in both tau mutation- and APP/presenilin mutation-driven transgenic mice that are used to model distinct aspects of Alzheimer pathology. CD11c+ cell recruitment is likely to be a translational pathology to AD, given prior evidence for both innate immune cell recruitment and dendritic cell marker upregulation in AD brain. With the emergence of multiple genetic links between innate immune dysregulation and AD, and recent clinical success of immune cell recruitment inhibitors in relapsing/remitting multiple sclerosis, these data suggest the hypothesis that blocking recruitment of dendritic cells into brain may be a promising therapeutic approach in AD.

Disclosures: **R.B. Nelson:** A. Employment/Salary (full or part-time):; Employee, Lundbeck Research USA. **I. Kadiu:** A. Employment/Salary (full or part-time):; Lundbeck Research USA. **L.K. Isaac:** A. Employment/Salary (full or part-time):; Employee, Lundbeck Research USA. **M.J. DenBleyker:** A. Employment/Salary (full or part-time):; Employee, Lundbeck Research USA. **S. Krzyzanowski:** A. Employment/Salary (full or part-time):; Employee, Lundbeck Research USA. **N. Breysse:** A. Employment/Salary (full or part-time):; Employee, Lundbeck

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Department of Veteran Affairs Merit Award BX001875

Title: Combined administration of resolvin E1 and lipoxin A4 resolves inflammation and prevents neurodegeneration in a murine model of Alzheimer's disease

Authors: *A. KANTARCI[1], I. CARRERAS[2,3,4], N. AYTAN[2,3,5], I. PALASKA[1], L. CRABTREE[6,2], B. G. JENKINS[5], A. DEDEOGLU[2,3,5]
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Abstract: Neurodegeneration in Alzheimer’s disease (AD) is closely related to inflammation in the brain. Markers of glial activation are elevated even before the development of amyloid (Aβ) deposition implying that neuroinflammation may have a causative effect in AD pathogenesis. Resolution of the inflammatory process is actively regulated by pro-resolving lipid mediators (resolvins and lipoxins). In this study, we tested the hypothesis that combined use of RvE1 and LXA4 will reverse the neuroinflammatory process associated with the AD pathology. 5xFAD transgenic mice were treated intraperitoneally starting at 1 month of age with RvE1 or LXA4 alone and in combination at a dose of 1.5 μg/kg, 3 times a week. As controls, untreated 5xFAD and WT groups were given the same volume of vehicle (saline with 1% ethanol). At 3 months of age, mice were euthanized and brains were collected. The left hemibrain was immunostained with antibodies to Aβ1-40 and Aβ1-42, GFAP and Iba1 to stain Aβ, astrocytes and microglia. The right hemisphere was used to quantitate the concentrations of Aβ40, Aβ42, RvE1, LXA4, and RvD2 by ELISA and the level of receptors for RvE1 and LXA4 (ALX/FPR1 and ERV1, respectively) by Western blot analysis. Combined therapy with RvE1+LXA4 decreased the levels of Aβ40 (compared to untreated 5xFAD mice) whereas RvE1 and LXA4 alone decreased the Aβ40 plaque burden. RvE1 treatment significantly lowered the Aβ42 plaque burden in

5xFAD treated mice. The ratio of activated/total microglia (A/T) and GFAP immunostaining significantly decreased in 5xFAD mice in response to combined LXA4+RvE1. The hippocampal concentrations of RvE1, LXA4 and RvD2 were significantly lower in 5xFAD mice compared to WT mice; treatment with RvE1 and LXA4 resulted in significant increases in the levels of RvE1, LXA4 and RvD2. The expression of the receptors ALX/FPR1 and ERV1 was significantly decreased in what group animals with AD. Machine learning tools were used for discrimination between the 4 groups of mice by algorithms to pick which of the various experimental parameters measured contributed the most to separation between the groups The attributes that contributed the most to the separation of groups were GFAP in cortex, GFAP in hippocampus, Aβ40 plaque burden, and Iba1 (A/T). Using these 4 parameters the combined treatment group was the closest to WT. The markers of inflammation (GFAP, Iba1) were better than the markers of Aβ pathology for discrimination between groups. These results suggested that the treatment with RvE1 and LXA4 impact the hippocampus and their combined use restores the levels of pro-resolution phase lipid mediators while reversing the neuroinflammatory process associated with AD.

Disclosures: **A. Kantarci:** None. **I. Carreras:** None. **N. Aytan:** None. **I. Palaska:** None. **L. Crabtree:** None. **B.G. Jenkins:** None. **A. Dedeoglu:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.19/K6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: small project fund, HKU

Title: Adiponectin suppresses amyloid-β(Aβ)-induced neuroinflammation in Alzheimer's disease via AMPK-NF-κB signaling pathway

Authors: *M. JIAN, R. C.-L. NG, K. CHAN
The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Background: Microglia-mediated neuroinflammation is an important contributor to the development of neurodegenerative diseases, including Alzheimer’s disease (AD). Extracellular deposition of amyloid-β (Aβ) is a key pathological characteristic of AD that can induce microglia activation causing neuroinflammation. Adiponectin (APN), an adipocyte-derived adipokine, exerts anti-inflammatory effect in both periphery and the brain. Our group has recently reported that APN deficiency leads to AD-like cognitive impairment and pathologies including microglia activation. However, the role of APN on microglia-mediated neuroinflammation in AD remains unknown. Here, we aim to determine whether APN can

inhibit oligomeric Aβ (AβO)-induced neuroinflammation in BV2 microglia cells and explore the underlying mechanism.
Methods: BV2 cells were pre-treated with APN before being treated with AβO prepared from human $A\beta_{(1-42)}$ peptide. Levels of pro-inflammatory cytokines were determined by the ELISA. mRNA and protein expressions were analyzed by RT-PCR and Western Blot. The morphology of microglia was evaluated by immunostaining. BV2-conditioned medium was used to treat hippocampal cell line (HT22) and cytotoxicity was assessed by MTT reduction.
Results: We found that APN receptor 1 and APN receptor 2 were expressed in BV2 cells. APN increased the level of AMPK phosphorylation and suppressed nuclear translocation of nuclear factor kappa B (NF-κB) induced by AβO. APN also inhibited releases of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) induced by AβO. Concordantly, blocking AMPK with compound C significantly abolished the anti-inflammatory effects of APN on AβO-treated BV2 cells. These indicated that APN suppressed microglia activation via AMPK-NFκB cascade. To further verify if APN altered the inflammatory state of microglia, we studied morphological changes of microglia upon APN and AβO treatment. We found that AβO treatment led to larger somata and shorter cytoplasmic processes as an amoeboid morphology of BV2 cells, whereas APN reduced the AβO-induced morphological changes and restored ramified quiescent microglia. Lastly, we studied if the anti-inflammatory effect of APN is protective to neurons. HT22 neuronal cells were incubated with conditioned medium prepared by AβO-treated BV2 cells. We found that conditioned medium from AβO-treated microglia was cytotoxic to HT22 neuronal cells whereas APN inhibited the cytotoxicity and enhanced HT22 cells survival.
Conclusions: APN can inhibit AβO-induced neuroinflammation in BV2 cells. Our results suggest that APN is a potential therapeutic agent to inhibit neuroinflammation in AD.

Disclosures: M. Jian: None. **R.C. Ng:** None. **K. Chan:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.20/K7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG048205

Title: Glia maturation factor colocalizes with NLRP3 inflammasome and inflammatory cytokines at the vicinity of amyloid plaques and neurofibrillary tangles in human Alzheimer’s disease brain

Authors: *A. ZAHEER[1,2], M. AHMED[1], S. P. GOVINDHASAMY[1], R. THANGAVEL[1,2], K. DURAISAMY[1,2], S. RAIKWAR[1], S. ZAHEER[1], S. IYER[1]

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the presence of intracellular neurofibrillary tangles (NFTs) containing an aggregated hyperphosphorylated microtubule-associated protein tau, and amyloid plaques (APs) comprised of beta amyloid. Glia maturation factor (GMF) is highly conserved brain specific pro-inflammatory protein, isolated and cloned in our laboratory has been shown to activate glial cells to produce toxic cytokines and chemokines leading to neuroinflammation and neurodegeneration in AD. However, the molecular mechanisms underlying GMF-induced neuroinflammtion and neurodegeneration are not clear. Here we hypothesized that the inflammatory reactions promoted by the NLRP3 inflammasomes are amplified and regulated by GMF in the pathogenesis of AD. To validate our hypothesis, we have analyzed the expression of GMF, inflammasome components and inflammatory cytokines in the AD and age-matched non AD brains. Tissue sections and lysates were prepared from the temporal cortex of human postmortem brains. Here we demonstrate an increased expression of the inflammasome components NLRP3, Caspase-1, IL-1β and IL-18 and GMF in the temporal cortex of the AD brains as compared to age-matched human non-AD brains. These inflammasome components and the pro-inflammatory cytokines co-localize with GMF in the vicinity and periphery of the amyloid plaques and NFTs. Our current data suggest that the neuroinflammation promoted by the NLRP3 inflammasome is amplified and regulated by GMF and significantly contributes to the pathogenesis of AD.

Disclosures: A. Zaheer: None. **M. Ahmed:** None. **S.P. Govindhasamy:** None. **R. Thangavel:** None. **K. Duraisamy:** None. **S. Raikwar:** None. **S. Zaheer:** None. **S. Iyer:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.21/K8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Chao Alzheimer Research Fund

Title: Characterization of monocyte phenotypes and gene expression profiles in Alzheimer's disease

Authors: *A. D. THOME[1,3], B. PASCUAL[4], D. R. BEERS[3], W. ZHAO[3], J. C. MASDEU[2], S. H. APPEL[3]
[1]Neurol., [2]Houston Methodist, Houston, TX; [3]Houston Methodist Neurolog. Inst., Houston, TX; [4]Dept. of Neurol., Houston Methodist Hosp., Houston, TX

Abstract: Innate and adaptive immune systems have pivotal and interdependent roles in neurodegenerative diseases such as Alzheimer's disease (AD). Both systems contribute to neuroinflammation and recent evidence collected from patients with AD suggest a pro-inflammatory micro-environment characterized by extensive microgliosis in the brain that is accompanied by increased pro-inflammatory cytokines levels in cerebrospinal fluid and serum. Animal models of AD have recapitulated these findings and resulted in these mechanisms becoming targets for immunomodulatory therapies. However, characterization in AD patients of peripheral innate and adaptive immune cells and their phenotypes lack sufficient detail. Our study describes specific peripheral immune cell alterations during disease pathoprogression, including immune cell populations, phenotypes, and gene expression profiles. Patients diagnosed with early mild cognitive impairment to late-stage AD were compared with age/gender matched healthy controls. Flow cytometry documented decreased numbers of classical monocytes (CD14+CD16-) with concomitantly increased numbers of intermediate (CD14+CD16+) and non-classical monocytes (CD14lowCD16+), and an increase in myeloid-derived suppressor cells (MDSC), as disease burden progressed. RNA analysis of peripheral blood mononuclear cells (PBMC) showed increased expression of CD16, M-CSF, IL6, IL-18, TNFα, and IL-1β in AD patients compared with controls. Additionally, increased RNA expression of these pro-inflammatory cytokines was also noted in peripheral monocyte/macrophage populations suggesting peripheral immune cell dysfunction. The altered number and gene expression of specific populations of PBMC and monocytes/macrophages promote a pro-inflammatory micro-environment that could contribute to the pathogenesis and progression of neurodegeneration in patients with AD. These data emphasize the role of peripheral immunity in AD and its possible modification by new therapies.

Disclosures: A.D. Thome: None. **B. Pascual:** None. **D.R. Beers:** None. **W. Zhao:** None. **J.C. Masdeu:** None. **S.H. Appel:** None.

Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.22/K9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA Merit Award # I01BX001875-01

Alzheimer's Drug Discivery Foundation

Title: Dual dose-dependent effects of fingolimod in a mouse model of Alzheimer's disease

Authors: *A. DEDEOGLU[1], N. AYTAN[2], J.-K. CHOI[3], V. BRINKMANN[4], J. K. BLUSZTAJN[2], L. CRABTREE[5], B. NGUYEN[6], N. KOWALL[7], B. JENKINS[3], I. CARRERAS[7]

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Abstract: There is evidence that lipid metabolism is abnormal in Alzheimer's disease (AD) brain. The abnormal sphingolipid metabolism in AD brains leads to the accumulation of pro-apoptotic and pro-inflammatory ceramides and sphingosine while levels of sphingosine 1-phosphate (S1P) that enhances cell proliferation and antagonizes apoptosis decrease. In AD, S1P levels decline in a region-specific manner during the course of the disease and its levels correlate well with the development of neurofibrillary tangles (NFT) and amyloid β (Aβ) pathology. Changes in S1P signaling may be central to the inflammatory and immune aspect of AD pathogenesis and the action of specific modulators of the S1P signaling system may improve AD-related pathology and behavior. One such modulator is Fingolimod, a structural analog of sphingosine that like sphingosine gets phosphorylated and activated *in vivo*. Fingolimod has been recently approved by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS). In RRMS Fingolimod prevents the infiltration of lymphocytes into the CNS and, after crossing the blood-brain-barrier, directly promotes remyelination and exerts neuroprotective effects on astrocytes. We have recently reported that Fingolimod, orally given to 5xFAD mice from 1-3 months of age, decreases the activation of microglia and reactive astrocytes, decreases Aβ levels, and increases neurogenesis. We expanded our original report with a dose response study of Fingolimod (0.03, 0.1, 0.3 and 1 mg/kg/day) in 5xFAD mice treated from 1-8 months of age. As controls, untreated 5xFAD and non-transgenic littermates were included (n=10). At 8 months of age, the learning and memory were analyzed in the water maze test. After that, mice were euthanized and blood and brains were saved for the analysis of complete blood count and for the analysis of AD-related pathology, by ELISA, immunohistochemistry and magnetic resonance spectroscopy. Our results showed that at 1mg/kg/day Fingolimod decreased the lymphocyte counts and the Aβ levels and that lower doses of Fingolimod decreased the activation of microglia and reactive astrocytes, increased neurogenesis, restored the hippocampal levels of GABA and glycerophosphocholine, and improved memory. These results demonstrate that Fingolimod treatment affects a number of different markers of AD pathology and behavior with the lowest dose used, 0.03 mg/kg/day, providing protection for the largest number of variables tested. Results also showed that,1 mg/kg/day dose had the largest effect on Aβ pathology that correlates with the levels of lymphocytes in the blood.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.23/K10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 5R01AG048993

ND EPSCoR State funding UND0021228

Title: Probiotic supplementation improved cognitive and intestinal function in a mouse model of Alzheimer’s disease

Authors: *H. KAUR[1], K. NAGAMOTO-COMBS[2], J. CLARK[1], C. K. COMBS[1]
[1]Dept. of Biomed. Sci., [2]Dept. of Pathology, Univ. of North Dakota, Grand Forks, ND

Abstract: It has been demonstrated that changes in intestinal microbiota may not only influence gastrointestinal function but also affect the central nervous system. An altered intestinal microbial ecosystem has been associated with the pathogenesis of various brain disorders in which inflammation is implicated including mood disorder, multiple sclerosis, and depression, to name a few examples. However, it is unclear whether alteration of the intestinal microbiota affects progression or inflammatory aspects of Alzheimer’s disease (AD), one of the most common dementing neurodegenerative diseases. In order to test this idea, littermate control wild type C57BL/6 mice were compared to the newly characterized APP knock-in transgenic mouse line that has the human Aβ sequence knocked in to the mouse APP gene along with three disease causing mutations (APP NL-G-F). The animals at 7 months of age were randomly divided into two groups and orally treated with vehicle (control) or probiotic (VSL#3) for 8 weeks. VSL#3 is a medical food containing 8 strains of live, freeze-dried lactic acid producing bacteria. The vehicle treated APP (NL-G-F) mice demonstrated impaired memory and increased anxiety-like behavior when compared to vehicle treated wild type mice using a cross maze and light-dark box behavioral test, respectively. This correlated with increased intestinal permeability in the vehicle treated APP (NL-G-F) but not wild type mice. However, no differences were observed in gastric emptying and intestinal motility in APP (NL-G-F) compared to wild type mice. Importantly, probiotic (VSL#3) supplementation to APP (NL-G-F) animals for 8 weeks significantly reduced intestinal mucosal permeability and improved memory performance. Our results support a role for intestinal microbes in the pathophysiology of AD and suggest that enrichment with beneficial bacteria could potentially help in treatment or prevention of AD. Further research is needed to understand the molecular mechanism of action attributed by these beneficial bacteria in CNS disorders.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.24/K11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH/NIA, R21AG054890

Cure Alzheimer's Fund

Title: ABCA7 haploinsufficiency compromises immune responses in mouse brains

Authors: *T. AIKAWA[1], Y. YAMAZAKI[1], M. TACHIBANA[2], M. R. JOHNSON[1], Y. A. MARTENS[1], M.-L. HOLM[1], C. ANDERSON[1], K. ISHIGURO[1], H. OUE[1], L. FELTON[1], B. GUOJUN[1], T. KANEKIYO[1]
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Abstract: *ABCA7* gene coding ATP-binding cassette transporter A7 is ranked as one of the top susceptibility loci for late-onset Alzheimer's disease (AD). Importantly, loss-of-function variants in *ABCA7* have also been shown to increase AD risk. Thus, it is critical to understand how decreased ABCA7 levels and/or diminished function contribute to AD pathogenesis. ABCA7 belongs to the ABC transporter family, which regulates the distribution of lipids/lipophilic molecules and the phagocytic pathway. Although accumulation and deposition of amyloid-β (Aβ) peptides in the brain are central events in AD, increasing evidence indicates that the immune system is significantly involved in the development and progression of the disease. While ABCA7 is abundantly expressed in microglia in the brain, contributions of ABCA7 to microglia-mediated immune system have not been fully understood. Thus, we investigated brain immune responses against peripheral lipopolysaccharide (LPS) stimulation in wild-type (WT) and *Abca7* heterozygous (*Abca7*$^{+/-}$) mice. To assess acute response of microglia, the mice were intraperitoneally treated with LPS at the age of 2 months and the number of Iba1-positive cells was histologically quantified in those mice 3.5 hours after the LPS injection. While LPS administration significantly increased the number of Iba1-positive microglia in both the cortex and hippocampus of WT mice, the effect was not detected in *Abca7*$^{+/-}$ mice. Furthermore, we found that LPS-induced mRNA expressions of pro-inflammatory cytokines including TNF-α, IL-6 and IL-1β were suppressed in the brains of *Abca7*$^{+/-}$ mice compared to WT mice. Because LPS stimulation activates microglia through Toll-like receptor 4 (TLR4), these results suggest that ABCA7 influences microglial functions by regulating TLR4-mediated pathways. The TLR4-

mediated microglial immune response likely has beneficial roles in stimulating phagocytosis in AD, although the excess activation of the pathway causes detrimental effects by releasing neurotoxic products. Thus, ABCA7 loss-of-function may disturb proper immune responses in microglia, which contributes to AD pathogenesis.

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Poster

126. Alzheimer's Disease: Neuroinflammation and Immune Action

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 126.25/K12

Topic: F.10. Food Intake and Energy Balance

Support: NIH Grant P01AG012411

UAMS S.T.O.P. Alzheimer’s Fund

Wingate Charitable Foundation

Arkansas Biosciences Institute

Roy & Christine Sturgis Charitable Trust

Title: Dysregulation of blood glucose levels by the hypothalamic-pituitary-adrenal axis in a model of Alzheimer's disease

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Abstract: Evidence for peripheral metabolic perturbations in Alzheimer’s disease (AD) has accrued in recent years, including an epidemiological comorbidity of AD and Type-2 diabetes mellitus (T2DM) and/or impaired glucose tolerance. Because cognitive deficits are prevalent in T2DM, the latter has been proposed to contribute to development of AD, but diabetics fail to accumulate amyloid β-peptide (Aβ) in the brain at any higher rate than controls. Previously our lab determined that male mice of the “BRI-Aβ42” transgenic line show significant impairment in glucose tolerance. Male BRI-Aβ42 mice overexpress $A\beta_{1-42}$ (the most pathogenic form of Aβ) within the CNS without overexpressing the entire amyloid precursor protein. This model provides a unique way to study hypotheses based on accumulation of $A\beta_{1-42}$, independent of APP

processing; it thus circumvents possible artifacts due to bioactivity of APP or its other cleavage products. Because the hypothalamic-pituitary-adrenal (HPA) axis can effectively regulate glucose homeostasis and is under CNS control, we sought to determine its contribution to Aβ effects on glucoregulation. We used adrenalectomy as a paradigm of primary adrenal insufficiency in male BRI-Aβ42 mice and wild-type littermates. Impaired glucose regulation was partially ameliorated both in basal glucose level and glycemic rise. Changes in insulin sensitivities were also observed due to adrenalectomy but not due to $A\beta_{1\text{-}42}$ expression. These results indicate that chronic activation of the HPA axis is a contributing factor in the development of impaired glucose tolerance and suggest that other mechanisms of glucoregulation also contribute.

Disclosures: R.D. Hendrix: None. **S.W. Barger:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); receives royalties from MilliporeSigma Inc. for the sales of secreted amyloid precursor protein.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.01/L1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grant-in-Aid for Scientific Research (C) from JSPS (22590936)

Grant-in-Aid for Scientific Research (C) from JSPS (26461274)

Title: Apomorphine as a novel drug for Alzheimer's disease targeting brain diabetes

Authors: *Y. OHYAGI[1,2,3], N. NAKAMURA[4], T. IMAMURA[4], A. WATANABE[3], N. FUJII[3]
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Abstract: Alzheimer’s disease (AD) is the major cause of dementia in the elderly people. At present, AD is understood as “type-3 diabetes” or “brain diabetes”, which means that diabetes mellitus (DM)-like pathogenesis may be promoted in AD brain. Many recent reports suggest that elevation of peripheral insulin resistance accelerates cognitive decline, and some DM drugs such as insulin, DPP-4 inhibitors, and GLP-1 agonists may improve cognitive function and AD pathology in AD mouse models. In 2011, we reported that apomorphine (APO), a dopamine receptor agonist for Parkinson’s disease (PD) patients, promoted degradation of intracellular amyloid beta-protein42 (Abeta42) and improved memory function, which was evaluated by Morris water maze test, in 3xTg-AD mice (Himeno et al., Ann Neurol, 2011). To further clarify

the mechanisms of APO effects, we performed DNA microarray analysis using cell culture and found that APO treatment may effect on the cell cycle and insulin signaling. Thus, we next checked the levels of insulin-degrading enzyme (IDE), a major intracellular Abeta-degrading enzyme, and serine-phosphorylated (pS^{616} and $pS^{636+639}$) insulin receptor substrate-1 (IRS-1), markers of cellular insulin resistance, by western blotting and immunohistochemistry. Proteins of IDE and pS^{616}/$pS^{636+639}$ IRS-1 increased in 13-month-old 3xTg-AD mice compared to non-Tg mice significantly (n=7). In addition, APO treatment increased IDE levels and decreased pS^{616}/$pS^{636+639}$ IRS-1 levels in neurons significantly, indicating that insulin resistance may be ameliorated and intraneuronal insulin signaling may be improved. Such effects of APO may contribute to improvement of memory function in 3xTg-AD mice. Finally, we studied the efficacy of APO treatment for AD patients in NHO Omuta Hospital. 1 mg of APO (minimum dose for PD) was subcutaneously injected once a week for 3 months to 5 AD patients. After APO treatments, there were no effects on mini-mental state examination (MMSE) scores, but there was apparent improvement of memory of words in AD assessment scale (ADAS)-Jcog tests. In a patient with moderate dementia, a cube drawing was clearly improved, indicating improvement of visuospatial agnosia or constructive apraxia. In conclusion, APO may improve neuronal insulin resistance and insulin signaling in AD mice, and brain diabetes may thus be a promising therapeutic target in AD.

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Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.02/L2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Council of Scientific and Industrial Research Grant (09/135/705/2014- EMR-I)

Title: Neuroprotective effect of tramadol in ICV-STZ induced sporadic dementia of Alzheimers type in rats

Authors: *D. K. DHULL, A. KUMAR
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Abstract: Alzheimer disease represents a major public health issue with limited therapeutic interventions. We explored the possibility of therapeutic approach by repurposing of tramadol in sporadic animal model of Alzheimer's type. Male SD rats were injected with streptozocin (3 mg/kg), bilaterally, through intracerebroventricular route. Drug treatment was given for 3 weeks post-surgery. The rats were sacrificed on the 21st day following the last behavioral test, and

cytoplasmic fractions of the hippocampus and pre-frontal cortex were prepared for the quantification of acetylcholinesterase, oxidative stress parameter and mitochondrial enzymes activity. Tramadol (5, 10 and 20 mg/kg, intraperitoneally) was used as treatment drug, and memantine (10 mg/kg, intraperitoneally) was used as a standard. Tramadol significantly attenuated behavioral, biochemical, and cellular alterations at low (5mg/kg) and intermediate (10mg/kg) dose, suggesting its neuroprotective potential in ICV-STZ treated rats. Surprisingly, tramadol (20 mg/kg) treatment reduced the survival of ICV-STZ treated rats to approximately 42% as compared to 72% survival rate of ICV-STZ treated rats. The neuroprotective effect of tramadol (10mg/kg) was comparable to memantine (10mg/kg). Our results indicate the effectiveness of tramadol in preventing cognitive impairment as well as mito-oxidative stress. Further, these findings reveal the possibility of tramadol as a therapeutic approach for sporadic Alzheimer disease.

Disclosures: D.K. Dhull: None. **A. Kumar:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.03/L3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Merit Award BX001875 to A. Dedeoglu

NIH R01 AG045031 to JK. Blusztajn

Title: Protective effects of 7,8-dihydroxyflavone on neuropathological and neurochemical changes in a mouse model of Alzheimer's disease

Authors: N. AYTAN[1], J.-K. CHOI[3], I. CARRERAS[4], L. CRABTREE[5], B. NGUYEN[2], M. LEHAR[2], *J. K. BLUSZTAJN[6], B. G. JENKINS[7], A. DEDEOGLU[4]
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Abstract: Interest in brain-derived neurotrophic factor (BDNF) was greatly enhanced when it was recognized that its expression is reduced in neurodegenerative disorders, especially Alzheimer’s disease (AD). BDNF signaling through the tropomyosin-related kinase B (TrkB) cellular receptor has a central role in promoting synaptic transmission, synaptic growth (i.e. synaptogenesis), and facilitating synaptic plasticity making the BDNF-TrkB signaling pathway

an attractive candidate for targeted therapies. Here we investigated the early effect of the small molecule TrkB agonist, 7,8 dihydroxyflavone, on AD-related pathology, dendritic arborization, synaptic density, and neurochemical changes in a 5xFAD mouse model of AD. In this study, 5xFAD mice and non-transgenic (WT) littermates were treated with 7,8-dihydroxyflavone (5 mg/kg, 3 days a week by intraperitoneal (i.p) injection) for 2 months starting at 1 month of age. We evaluated the effect of 7,8 dihydroxyflavone treatment on Aβ42 and Aβ40 levels using ELISA. Aβ42 and Aβ40 plaque deposition were quantified with immunohistochemical staining. Changes in dendritic spine density and total spine number were analyzed using Neurolucida. Doublecortin (DCX) positive neurons were counted using stereology to quantify neurogenesis. Brain neurochemical changes were quantified using magnetic resonance spectroscopy. We found that 7,8 dihydroxyflavone treatment decreased Aβ plaque deposition, and protected against glutamate loss and choline increase but had no impact on neurogenesis and spine density at 3 months of age in a 5xFAD mouse model of AD. Our study shows that 7,8 dihydroxyflavone treatment at the earliest stages of AD-like pathology in a mouse model prevents and/or delays several pathophysiologic processes associated with this disease.

Disclosures: **N. Aytan:** None. **J. Choi:** None. **I. Carreras:** None. **L. Crabtree:** None. **B. Nguyen:** None. **M. Lehar:** None. **J.K. Blusztajn:** None. **B.G. Jenkins:** None. **A. Dedeoglu:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.04/L4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG032611

NIH Grant R01 AG020197

NIH Grant R01 NS077239

Title: Prophylactic active tau immunization prevents both tau and amyloid-beta pathology in 3xTg mice

Authors: Y. LIN[1], H. B. RAJAMOHAMEDSAIT[1], S. RASOOL[1], W. J. RAJAMOHAMEDSAIT[1], *E. M. SIGURDSSON[2]
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Abstract: Amyloid-β (Aβ) and tau lesions are thought to be related in Alzheimer’s disease with several studies suggesting that the former can lead to the latter. We have previously shown that

immunization with tau peptides or antibodies removes tau aggregates and improves cognition in preclinical studies, which has been confirmed and extended by many groups and led to several clinical trials. Here we show that prophylactic tau immunization in 3xTg mice not only clears abnormal tau in the brain but also extensively clears Aβ plaques, suggesting that tau pathology can promote Aβ deposition.

Transgenic (3xTg) and wild-type (wt) mice of the same strain background received four s.c. immunizations of 100 μg of Tau379-408[P-Ser396,404] in 100 μl alum adjuvant from 2-6 months of age (n=41). Controls received adjuvant alone (n=36). The mice developed a robust IgG response and less pronounced IgM response in both male and female 3xTg and wt mice, compared to controls. Notably, the mice maintained high antibody levels until the end of the study at 22 months of age. Surprisingly, cognitive impairments were not detected in the 3xTg mice at 20-22 months of age, compared to wt controls. No cognitive benefits were observed with the immunotherapy, presumably because the mice were not impaired. Brain immunohistochemical analyses revealed pronounced tau and Aβ pathology, primarily in the subiculum/CA1 region, which was therefore the focus of analysis. The therapy reduced PHF1- and MC1-immunoreactive (IR) tau aggregates by 70% and 64% overall (males and females; $p<0.01$), and by 78% and 86% in the females ($p<0.05$-0.01), respectively, compared to 3xTg controls. Likewise, western blot analysis revealed a clearance of tau in the immunized mice (insoluble human tau: 37% overall, $p<0.05$; 45% in females, $p<0.05$). Furthermore, subicular Aβ plaque burden was reduced by 81% overall ($p<0.0001$), by 50% in males ($p<0.05$), and by 97% in females ($p<0.0001$). GFAP IR was greater in 3xTg mice compared to wt mice ($p<0.01$) but the therapy did not affected astrogliosis. Likewise, microgliosis was more pronounced in 3xTg mice than in wt mice ($p<0.01$) but the immunotherapy reduced it in the Tg mice ($p<0.05$). Microhemorrhages were seen more often in 3xTg mice compared to wt mice ($p<0.05$), and were reduced in the treated Tg mice compared to their Tg controls ($p<0.05$).

In summary, these results indicate that prophylactic tau immunization reduces not only tau pathology but also Aβ burden, which supports the view that tau and Aβ pathologies are synergistic, and the promise of this therapeutic approach. Furthermore, gradual removal of these lesions reduces microgliosis and microhemorrhages, which may provide additional benefits.

Disclosures: Y. Lin: None. **H.B. Rajamohamedsait:** None. **S. Rasool:** None. **W.J. Rajamohamedsait:** 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

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.05/L5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AbbVie

Title: Chronic administration of the spingosine-1-phoshate receptor 5 agonist A-971432 improves cognition and reduces soluble aβ in the SAMP8 mouse model of Alzheimer's disease

Authors: *E. VAN DER KAM[1], S. A. FARR[3], J. W. BROWN[4], J. VAN BERGEIJK[2], M. L. NIEHOFF[5], J. E. MORLEY[6]
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Abstract: Sphingosine-1-phophate (S1P) is highly expressed in endothelial cells in the blood-brain barrier (BBB) and the brain. S1P has 5 subtype receptors (S1P1-5) which are involved in a host of cellular processes including cell proliferation, migration, survival, and regulation of neurological function. Reports indicate that a novel selective and bio-available S1P5 compound, A-971432, is highly effective in reversing brain lipid accumulation, age-related cognitive decline, and protects BBB integrity; features that make it attractive for the potential treatment of AD. In the current study, ten month old male SAMP8 mice were administered A-971432 via daily oral gavage (2mL/kg) at 0, 0.03, 1 or 3 mg/kg for 10 weeks. A young SAMP8 control group received vehicle for 10 weeks. Mice were tested in novel object recognition (NOR) and activity during weeks 7/8 of treatment and T-maze foot shock avoidance during weeks 9/10 of treatment. At the end, brain tissue was collected for ceramide, exposures levels, Aβ, and Tau biochemical analysis. In NOR, 12 month old mice that received 1 mg/kg A-971432 spent significantly more time with the novel object during the 24 hour retention test in comparison to vehicle-treated mice. There was no difference in total exploration time during testing. In the T-maze, the 12 month old mice that received 0.03 and 1 mg/kg took significant fewer trials to make one avoidance than the 12 month old vehicle. In the T-maze retention test, treatment with 0.03 and 1 mg/kg also resulted in significantly fewer trials to make 5 avoidance in 6 consecutive trials. The highest dose was without effect, but showed considerable variation in the response and exposure. Biochemical analysis of the brain indicated increased ceramide (C18:0), RAB-soluble (monomeric soluble) Aβ40, and Aβ42 in vehicle-treated old SAMP8 mice compared to young vehicle-treated mice. The doses of 0.03 and 1mg/kg significantly lowered ceramide, Aβ40, and Aβ42 levels in these mice. A similar profile was observed with 3mg/kg, except it did

not significantly reduce ceramide. There were no age (young vs. old) differences or treatment effects on Tau levels observed. The data presented here indicate 10wk administration of A-971432 significantly improved learning and memory in the SAMP8 model of AD. Biochemical analysis found that doses that significantly improved cognition also significantly lowered ceramide, consistent with the mechanism of action of this drug. Furthermore, these same doses also significantly lowered soluble Aβ40 and Aβ42, suggesting the cognition-improving effect observed with A-971432 in SAMP8 mice may be mediated by its Aβ-lowering action, in addition to its activity on ceramide.

Disclosures: **E. Van Der Kam:** A. Employment/Salary (full or part-time):; AbbVie. **S.A. Farr:** 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.; AbbVie. **J.W. Brown:** A. Employment/Salary (full or part-time):; AbbVie. **J. van Bergeijk:** A. Employment/Salary (full or part-time):; AbbVie. **M.L. Niehoff:** 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.; AbbVie. **J.E. Morley:** 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.; AbbVie.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.06/L6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: International Group of Neuroscience Initiative "Citizen Science for the common good".

Title: Reconstructing and strengthening networks affected by oxidative damage with EEG-triggered-TMS: Inducing very small, long-range electric signals in macromolecular prenetworks

Authors: *J. F. GOMEZ-MOLINA[1], ***J. F. GOMEZ-MOLINA**[1], U. M. RICOY[2], C. VELEZ-PARDO[3], M. JIMENEZ DEL RIO[5], M. CORREDOR[4], G. PERRY[6]
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Abstract: INTRODUCTION. 1. There is strong evidence that oxidative damage is the initial cytopathology in neurodegenerative diseases like Alzheimer (Perry et al. 2016, 2015) and Parkinson (Jimenez Del Rio, Velez-Pardo 2015) disease. In order to determine the sequence of events leading to neuronal oxidative damage and the source of the increased oxygen radicals we need a new unified treatment. The causes are not centralized but distributed in many mechanisms (e.g. RNA-based redox metal binding, RNA oxidation on protein synthesis rate, phosphorylation control). 2. Cytoskeletal changes are also at the origin of developmental and degenerative diseases; their electrical properties (resonance) has been reported (Jelinek and Pokorny 2001). 3. Pulsed electric fields can modify the molecular conformation of antioxidants and enhance antioxidant properties (Zhang et. al. 2015, Odriozola 2009). 4. Gamma frequency entrainment can reduce amyloid load (Iaccarino, Tsai 2016). METHODS. Circuit-System dynamics. HYPOTHESIS. 1. Electrical changes in the properties and signals of cortical regions -associated to oxidative damage in macromolecules- might be the target for diagnosis techniques and treatments (fig 1). 2. Macromolecular networks are “pre-neural networks”: on the first ones, the trajectories of very-small electric signals execute computational searching processes where many potential networks are evaluated in order to select the ones that optimizes neural communication and control resources (e.g. algorithms for minimum cost, maximum flow). 3. EEG-triggered TMS can amplify theta-Gamma electrical signals (Gomez-Molina et. al 2016) and in this way guide the formation of networks according to the will action (Llinas, 2001). CONCLUSIONS. Friendly forms of brain-computer interfaces and brain electric stimulation can be defined as those that respect the autonomy, integrity and expression of high brain centers even at the very-small signal level. Multi-disciplinary studies are needed to define these design criteria.

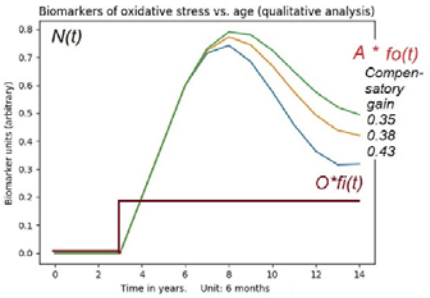

Fig. (Hyper)compensatory changes activated by oxidative stress can reduce oxidative stress in late phases of Alzheimer disease.
A Nunomura, G Perry, G Aliev, K Hirai,... Robert B Petersen, Mark A Smith 2001 Oxidative damage is the earliest event in Alzheimer disease Journal of Neuropathology & Experimental Neurology Vol 60 Issue 8 Pages 759-767

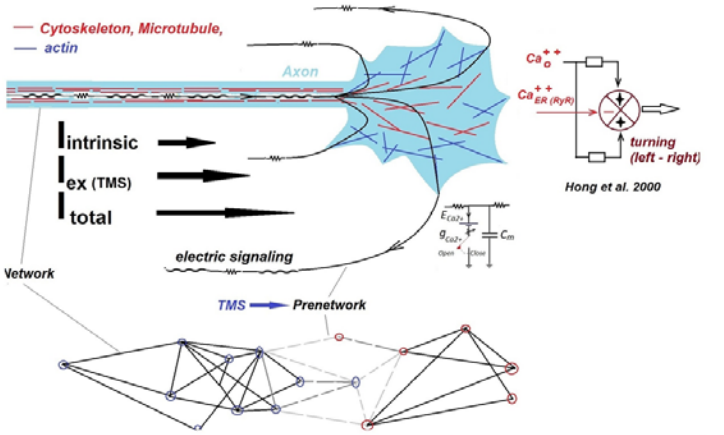

Fig. 2. The concept of Network and Prenetwork (Network in construction). TMS can induce currents in selected prenetworks.

Disclosures: J.F. Gomez-Molina: None. **U.M. Ricoy:** None. **C. Velez-Pardo:** None. **M. Jimenez del Rio:** None. **M. Corredor:** None. **G. Perry:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.07/L7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SATT AxLR Maturation Grant

Title: A novel phosphinolactone compound, OZP002, positive modulator of sigma-1 receptor, is neuroprotective in non-transgenic and transgenic mouse models of Alzheimer's disease

Authors: *T. MAURICE[1], J.-N. VOLLE[2], M. STREHAIANO[1], C. PEREIRA[1], C. LABORDE[2], D. VIRIEUX[2], J.-L. PIRAT[2]
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Abstract: The σ_1 receptor (S1R) is expressed in neurons and glial cells, mainly at mitochondria-associated endoplasmic reticulum (ER) membranes (MAMs). S1R chaperones several partner proteins, including BiP. Upon cellular stress or via agonist stimulation, S1R dissociates from BiP and binds IP_3 receptor, enhancing calcium entry into mitochondria. It plays a major role in cellular homeostasy and cytoprotection. We previously demonstrated its importance in Alzheimer's disease related neurodegenerative processes and identified the symptomatic and neuroprotective potentials of several S1R agonists. Recently, some compounds were described, acting as positive allosteric modulators of S1R (S1R PAMs). Although the biochemical characterization of PAM binding to S1R has not yet been documented, these compounds presented S1R-mediated anti-amnesic and anti-inflammatory activities. We here described a novel phosphinolactone, OZP002, that acts as a S1R PAM. The drug did not inhibit [^{3}H](+)-pentazocine binding but its antidepressant activity in the forced swim test was blocked by the S1R antagonist NE-100 or in S1R KO mice. The drug potentiated the antidepressant effect of the SR1 agonist igmesine, confirming its S1R PAM activity. In mice tested for Y-maze alternation or passive avoidance, OZP002 prevented scopolamine-induced learning deficits, in a NE-100 sensitive manner. Pre-administered IP before an ICV injection of amyloid Aß25-35 peptide, a pharmacological model of Alzheimer's disease, OZP002 prevented the learning deficits induced by the peptide after one week in the Y-maze, passive avoidance and object recognition tests. Biochemical analyses of the mouse hippocampi showed that OZP002 significantly decreased Aß25-35-induced increases in reactive oxygen species, lipid peroxidation, Bax TNFa and IL-6 levels. It also alleviated Aß25-35-induced decreases in synaptophysin level and choline acetyltransferase activity. Moreover, chronically administered in APPswe mice during 2 months, OZP002 prevented learning deficits (in all tests plus place learning in the water-maze) and increased biochemical markers. The present data identified OZP002 as a novel potent S1R PAM, with anti-amnesic and neuroprotective potential in mouse models of Alzheimer's disease.

Disclosures: **T. Maurice:** None. **J. Volle:** None. **M. Strehaiano:** None. **C. Pereira:** None. **C. Laborde:** None. **D. Virieux:** None. **J. Pirat:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.08/L8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI JP22500320

NIH Grant 1R01NS076794-01

Title: Combination therapy with (-) epigallocatechin-3-gallate and ferulic acid effectively modifies Alzheimer-like pathology

Authors: *T. MORI[1], N. KOYAMA[1], J. TAN[2], T. SEGAWA[3], M. MAEDA[3], T. C. TOWN[4]
[1]Dept. of Biomed. Sci., Saitama Med. Ctr. and Univ., Kawagoe, Saitama, Japan; [2]Silver Child Dev. Ctr., Dept. of Psychiatry and Behav. Neurosci., Univ. of South Florida, Tampa, FL; [3]Immuno-Biological Labs. Co., Ltd., Fujioka, Gunma, Japan; [4]Zilkha Neurogenetic Inst., Dept. of Physiol. and Biophysics, USC, Los Angeles, CA

Abstract: Nutraceuticals or naturally-occurring dietary compounds with beneficial properties, are well tolerated and hold promise as Alzheimer's disease (AD) therapeutics. We identified two candidates with complementary anti-amyloidogenic mechanisms of action: (-)-epigallocatechin-3-gallate (EGCG) and ferulic acid (FA), and examined whether combination therapy further modifies AD-like pathology *vs.* single treatment with either compound. Commencing at 12 months of age, we orally administered EGCG and/or FA (all at 30 mg/kg) or vehicle once daily for 3 months to the PSAPP transgenic mouse model of cerebral amyloidosis. At 15 months of age, combination therapy synergistically remediated most behavioral outcome measures *vs.* either single treatment. Moreover, EGCG plus FA-treated PSAPP mice had further amelioration of brain parenchymal and cerebral vascular β-amyloid deposits and decreased abundance of amyloid β-protein species compared to EGCG or FA treatment alone. Combination therapy elevated nonamyloidogenic soluble amyloid β-protein precursor (APP)-α and α-secretase candidate (a disintegrin and metalloproteinase domain-containing protein 10) and downregulated expression of amyloidogenic β-carboxyl-terminal APP fragment and β-secretase candidate (β-site APP cleaving enzyme 1). In concert, the ratio of β-carboxyl-terminal APP fragment to α-carboxyl-terminal APP fragment was decreased. *In toto,* combined treatment shifted APP cleavage toward the non-amyloidogenic pathway. Additional co-treatment effects included amelioration of neuroinflammation, oxidative stress, and synaptotoxicity. Therefore, we offer

pre-clinical evidence that combination therapy with EGCG and FA is a promising AD therapeutic approach.

Disclosures: **T. Mori:** None. **N. Koyama:** None. **J. Tan:** None. **T. Segawa:** None. **M. Maeda:** None. **T.C. Town:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.09/L9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: TAK-071, a positive allosteric modulator of M_1 muscarinic acetylcholine receptor, induces a c-Fos expression pattern similar to that by xanomeline in mouse brain

Authors: *T. MANDAI, M. KASAHARA, E. KURIMOTO, M. TANAKA, M. SUZUKI, A. NAKATANI, H. KIMURA
Takeda Pharmaceut. Co. Limited, Fujisawa/ Kanagawa, Japan

Abstract: Activation of M_1 muscarinic acetylcholine receptors (M_1R) could be an effective therapeutic approach for the treatment of Alzheimer's disease (AD) and schizophrenia. Xanomeline, an M_1R/M_4R agonist, improved cognitive function in patients with AD and schizophrenia, although its clinical development was discontinued due to side effects. Recently, we discovered a novel M_1R selective positive allosteric modulator, TAK-071, which reduced scopolamine-induced cognitive impairments with a wide therapeutic margin in rats. A detailed comparison of the pharmacological profiles of TAK-071 and xanomeline using relevant animal models was considered to further assess the therapeutic potential of TAK-071 in humans. However, as shown in this study and reported by others, xanomeline induced sedation at doses equal to or even lower than those required to improve cognition in rodents. As the sedative effects of xanomeline have the potential to affect the results of behavioral studies, we compared the pharmacological effects of xanomeline and TAK-071 on brain c-Fos expression in mice. Xanomeline (3 mg/kg s.c.) significantly increased c-Fos expression in several prefrontal areas, hippocampal formation, amygdala, and nucleus accumbens, but not in the orbital cortex, caudate putamen, or claustrum. TAK-071 (1 mg/kg p.o.) significantly increased c-Fos expression in brain regions similar to those of xanomeline, and in the orbital cortex and claustrum. When donepezil (3 mg/kg p.o.) was co-administrated to increase levels of acetylcholine in the brain, TAK-071 (1 mg/kg p.o.) increased the c-Fos expression in the same brain regions more robustly than when it was administered alone. These results suggest that TAK-071 and xanomeline modulate common, but not identical, neural pathways in the mouse brain. TAK-071 may have the potential to reduce cholinergic-related deficits in neuropsychiatric disorders such as AD, dementia with Lewy body (DLB), and schizophrenia. TAK-071 is currently in clinical development (ClinicalTrials.gov,

Identifier: NCT02769065).
T Mandai and M Kasahara contributed equally to this work.

Disclosures: **T. Mandai:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Kasahara:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **E. Kurimoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Tanaka:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Suzuki:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **A. Nakatani:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Kimura:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.10/L10

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: An approach to discover BDNF-inducible AMPA receptor potentiators with lower agonistic effects based on the *In vitro* characterization of three AMPA receptor potentiators, LY451395, HBT1, and OXP1

Authors: *A. KUNUGI, Y. TAJIMA, H. KUNO, S. SOGABE, H. KIMURA
Takeda pharmaceutical company, Fujisawa-Shi / Kanagawa, Japan

Abstract: Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor (AMPA-R) potentiators with brain-derived neurotrophic factor (BDNF)-induction potential could be promising as therapeutic drugs for neuropsychiatric diseases. However, BDNF-inducible AMPA-R potentiators such as LY451646 and LY451395 carry risks of narrow bell-shaped dose-responses and seizure. Interestingly, LY451395 showed an agonistic effect in rat cortical primary neurons, but not in a cell line expressing AMPA-Rs, in Ca^{2+} influx assays. Thus, we decided to establish screening strategies to discover novel BDNF-inducible AMPA-R potentiators with lower agonistic effects. From our chemical library of AMPA-R potentiators, we discovered two unique BDNF-inducible AMPA-R potentiators with lower agonistic effects using a Ca^{2+} influx assay and primary neurons: 2-(((5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetyl)amino)-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide (HBT1) and (3S)-1-(4-tert-butylphenyl)-N-((1R)-2-(dimethylamino)-1-phenylethyl)-3-isobutyl-2-oxopyrrolidine-3-carboxamide (OXP1). The mode of HBT1 and LY451395 binding to a pocket in the ligand binding domain (LBD) of AMPA-R differed; HBT1, but not LY451395, formed hydrogen bonds with S518 and S750 in the LBD. OXP1 may bind to a cryptic binding pocket on AMPA-R. Interestingly, co-stimulation with HBT1 and OXP1 in the absence of agonist robustly activated

AMPA-R in primary neurons. Thus, the mode of action underlying the activation of AMPA-R by small molecule compounds seemed to be more complicated than once thought. Here we propose approaches to discover BDNF-inducible AMPA-R potentiators with lower agonistic effects based on a careful consideration of the relationship between binding site/mode and functional outcome of HBT1, OXP1, and LY451395. These approaches to optimize HBT1-site binders or OXP1-site binders may lead to the discovery of novel BDNF-inducible AMPA-R potentiators with lower risks of bell-shaped dose-responses and seizure.

Disclosures: **A. Kunugi:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **Y. Tajima:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Kuno:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **S. Sogabe:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Kimura:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.11/M1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: TAK-071, a novel muscarinic M_1 receptor positive allosteric modulator, regulates quantitative EEG power spectra in a scopolamine challenge paradigm in monkeys

Authors: *E. KURIMOTO, M. NAKASHIMA, H. KIMURA, M. SUZUKI
Res., Takeda Phamaceutical Co. Limited, Fujisawa, Japan

Abstract: Activation of the muscarinic M_1 receptor (M_1R) is a promising approach to improve cognitive deficits associated with cholinergic dysfunction in Alzheimer's disease (AD) and dementia with Lewy body (DLB). TAK-071 is an M_1 selective positive allosteric modulator (PAM). A study in rats found that it improved cognitive deficits induced by scopolamine, a non-selective muscarinic receptor antagonist, and had a wide margin of safety and fewer side effects, including diarrhea. This study explores the possibility of using analsysis of quantitative electroencephalograms (qEEG) with and without a scopolamine challenge as a non-invasive translational biomarker in cynomolgus monkeys. Scopolamine has been reported to increase theta and delta power bands, and to decrease the alpha power band in healthy humans. Scopolamine (25-100 μg/kg s.c.) dose-dependently increased alpha, theta, and delta power bands in cynomolgus monkeys. The effects of TAK-071 on the scopolamine (25 μg/kg s.c.)-induced qEEG spectra changes were examined using an acetylcholinesterase inhibitor, donepezil, and an M_1/M_4R agonist, xanomeline, as comparators. TAK-071 (0.3-3 mg/kg p.o.), donepezil (3 mg/kg p.o.) and xanomeline (1 mg/kg s.c.) suppressed the scopolamine-induced increases in alpha,

theta, and delta power bands. TAK-071 at 1 and 3 mg/kg also slightly reduced alpha and theta power bands in the absence of a scopolamine challenge. These results suggest that scopolamine-induced changes in qEEG, particularly in theta and delta power bands, may serve as translational biomarkers for the effects of compounds such as TAK-071 in diseases associated with low-cholinergic tone. TAK-071 is currently in clinical development (ClinicalTrials.gov, Identifier: NCT02769065).

Disclosures: **E. Kurimoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Nakashima:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Kimura:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Suzuki:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.12/M2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: *In vivo* characterization of TAK-071, a novel muscarinic M_1 receptor positive allosteric modulator

Authors: *H. KIMURA, E. KURIMOTO, T. MANDAI, Y. SHIMIZU, A. SUZUKI, M. SUZUKI, M. TANAKA, M. YAMADA, H. SAKAMOTO, Y. SAKO
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Abstract: Muscarinic M_1 receptors (M_1R) are a promising target for CNS disorders with cholinergic deficits such as Alzheimer's disease and dementia with Lewy Body. We discovered TAK-071, a novel selective M_1R positive allosteric modulator (M_1PAM). TAK-071 had an inflection point (IP)-value of 2.7 nM, and showed an α-value of 199 for human M_1R with more than 3700-fold selectivity over other muscarinic receptor subtypes. Tonic activation of M_1Rs is known to produce neuronal excitability through three actions; depolarizing the resting membrane potential (RMP), suppressing the afterhyperpolarization (AHP) that follows the spike, and revealing the afterdepolarization (ADP) that can initiate repetitive firing. TAK-071 selectively induced ADP in layer 5 pyramidal neurons. Next, we characterized the *in vivo* profile of TAK-071 and compared it to that of donepezil, an acetylcholine esterase inhibitor. Activation of M_1R by M_1PAMs in the brain was assessed by measuring inositol monophosphate (IP1) levels in the hippocampus. TAK-071 significantly induced hippocampal IP1 production in rats and mice, but not in M_1R knockout mice. Similar to donepezil, TAK-071 reduced the cognitive deficit induced by scopolamine, a non-selective muscarinic receptor antagonist, in rats, but had no effect on time-dependent forgetting in a novel object recognition test. We also characterized

cholinomimetic effects of the compound, such as diarrhea, fasciculation, lacrimation, miosis, and salivation in rats. Donepezil induced all these signs, while TAK-071 induced only diarrhea. TAK-071 improved cognitive function at 0.3 mg/kg, PO and it induced diarrhea at 10 mg/kg, PO in rats. TAK-071 had a wide margin between doses leading to cognitive improvement and diarrhea induction. These results suggest that TAK-071 has promising therapeutic potential for CNS disorders, and is currently in clinical development (ClinicalTrials.gov, Identifier: NCT02769065).

Disclosures: H. Kimura: A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **E. Kurimoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **T. Mandai:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **Y. Shimizu:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **A. Suzuki:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Suzuki:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Tanaka:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **M. Yamada:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **H. Sakamoto:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited. **Y. Sako:** A. Employment/Salary (full or part-time):; Takeda Pharmaceutical Company Limited.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.13/M3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: ORGS Grant

Title: Neuroprotective effects of liraglutide on streptozotocin induced neurodegeneration in Alzheimer's disease mouse model

Authors: *L. PALADUGU[1,5], A. AL-GHARAIBEH[1,5], N. KOLLI[1,5], C. LEARMAN[1,5], T. C. HALL[1,5], R. L. CULVER[1,5], L. LI[2], J. ROSSIGNOL[1,3], P. MAITI[1,5,4], G. L. DUNBAR[1,4,5]
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Abstract: Recent clinical and epidemiological studies support that diabetes mellitus (DM) is one of the strong risk factors for the development of Alzheimer’s disease (AD). A definitive causal link between these two diseases has not been elucidated yet. The use of insulin cell toxin,

Streptozotocin (STZ), when injected via an intracerebroventricular (icv) route into the mice, develops an insulin resistant brain state (IRBS) and represents a non-transgenic or sporadic AD model (SAD) with a number of AD like neuropathological and cognitive features. This study aims at exploring the cognitive, neuroinflammatory, neurodegenerative, and insulin signaling dysfunction caused by STZ, with possible neuroprotection by an anti- diabetic drug, Liraglutide (LIR) in both transgenic 5xfamilial AD (5XFAD) and SAD models. Three month old 5XFAD and age-matched, wild-type mice were given a single icv injection of STZ, and were subsequently injected with LIR, intraperitoneally (IP), once a day for thirty days. After subjecting these mice to a series of behavioral tests including open field, object recognition and passive avoidance tests, the extent of neurodegeneration, amyloid beta (Aβ) plaque load, immunoreactivity (IR) of activated astrocytes (GFAP), activated microglia (Iba-1) and the expression of key proteins associated with insulin signaling pathway were investigated in the cortical and hippocampal regions of the brain tissue via immunohistochemical and Western Blot studies. Histological examination of the cortical and the hippocampal regions of the brain tissue indicate that treatment with LIR protected against STZ - induced neuroinflammatory responses in both models. Western blot analysis indicated that LIR decreased the Aβ plaque load in both models. LIR also improved the insulin signaling PI3/AKT pathway in the brain by increasing the levels of insulin degrading enzyme (IDE), the phosphorylation of Insulin receptor while reducing the phosphorylation of glycogen synthase kinase (GSK3β). Our results indicate that LIR, a GLP-1 receptor analog, has potential to serve as an anti-inflammatory and anti-amyloid agent for the treatment of AD.

Disclosures: L. Paladugu: None. **A. Al-Gharaibeh:** None. **N. Kolli:** None. **C. Learman:** None. **T.C. Hall:** None. **R.L. Culver:** None. **L. Li:** None. **J. Rossignol:** None. **P. Maiti:** None. **G.L. Dunbar:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.14/M4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Coins for Alzheimer’s Research Trust

NIH grant 5R25GM077634

NSF COMPASS grant 1356582

Alzheimer’s Drug Discovery Foundation

NC Space Grant/NASA Scholarship Program

UNC President's Strategic Initiatives Reserve Fund

Title: Different neurotherapeutic actions of the weak cathepsin B inhibitors N-carbobenzyloxy-L-phenylalanyl-L-alanyl-diazomethylketone (PADK) and 2S,3S-trans-epoxysuccinyl-L-leucylamido-3-methylbutane ethyl ester (E64d; aloxistatin) may be due to their dissimilar potencies for blocking the calcium-activated protease calpain that has been linked to both Alzheimer's disease and traumatic brain injury

Authors: *H. W. ROMINE[1], M. C. PAIT[2], K. RENTSCHLER[3], K. SMITH[3], A. EDWARDS[3], C. COLVIN[3], B. SIFFORD[3], Y. ABUMOHSEN[3], R. MASTERS[3], D. BUTLER[4], B. A. BAHR[5]
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Abstract: Cysteine protease inhibitors have long been part of research programs for developing therapeutics for Alzheimer's disease (AD) and other disorders (Vanderklish & Bahr 2000 IJEP 81:323; Trinchese et al. 2008 J Clin Invest 118:2796; Saatman et al. 2010 Neurotherapeutics 7:31; Pišlar & Kos 2013 Mol Neurobiol 43). Among the low potency inhibitors, the cathepsin B (CatB) and L inhibitor Z-Phe-Ala-diazomethylketone (PADK) exhibits a very weak CatB IC_{50} of 8-10 μM, but curiously PADK up-regulates CatB activity via the enzyme's active site (i.e. blocked by the potent CA074 inhibitor) and elicits protective Aβ42 clearance and improved performance in a novel spatial memory task in APPSwInd mice, as previously correlated with improved episodic memory in APP-PS1 mice (Butler et al. 2011 PLoS ONE 6:e20501). Other protective CatB-enhancing compounds were found to have no CatB inhibitory action (Viswanathan et al. 2012 ACS Med Chem Lett 3:920). In contrast, the weak CatB inhibitor E64d with a 14 μM IC_{50} (Jeon et al. 2016 Eur J Med Chem 121:433) has been implicated as an AD and TBI treatment through the inhibition of CatB (Hook et al. 2008 JBC 283:7745 and 2015 Front Neurol 6:178). Comparing their ability to block calcium-induced cytoskeletal breakdown using monoclonal anti-αII spectrin, 10-30 μM PADK exhibited little if any inhibition, whereas 1-10 μM E64d significantly reduced the 150-kDa spectrin breakdown product (SBDP) and 30 μM E64d completely blocked it. Similar results were found with antibodies against calpain's cleavage site that forms SBDP, a marker of pathogenic calpain activity linked to ischemia, TBI, and AD (Vanderklish & Bahr 2000; Peneda et al. 2004 Brain Pathol 14:202). E64d blocked the SBDP proteolytic event in brain samples with a 3.9 μM IC_{50} (ANOVA $p<0.01$), similar to its reported potency for blocking calpain (Hwang et al. 1992 J Med Chem 35:2048). These results point to disparate actions: For PADK, 1-3 μM on brain slices increased the 30-kDa active form of CatB, an Aβ42-degrading protease that reduces disease parameters in four AD mouse models (Mueller-Steiner et al. 2006: Neuron 51:703; Butler et al. 2011; Wang et al. 2012: JBC 287:39834), and this is noted as being consistent with studies showing that exercise elevates CatB, correlating with improved memory in humans, and may prevent or slow AD onset (Moon et al. 2016 Cell Metab 24:332). For E64d its dual inhibitory effect on calpain and CatB may explain its results in the distinct AD and TBI models since 1) calpain plays a role in these neurodegenerative disorders and 2) a calpain-cathepsin cascade has been implicated in AD (Yamashima 2016 Ageing Res Rev 32:169), a pathway perhaps underlying the later stages of neuronal death.

Disclosures: **H.W. Romine:** None. **M.C. Pait:** None. **K. Rentschler:** None. **K. Smith:** None. **A. Edwards:** None. **C. Colvin:** None. **B. Sifford:** None. **Y. Abumohsen:** None. **R. Masters:** None. **D. Butler:** None. **B.A. Bahr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.15/M5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: HDL subclass and inflammation marker in AD and MCI: STOP-Dementia project

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Abstract: BACKGROUND:
High density lipoprotein (HDL) and apolipoprotein A-I (A-I) have been shown to promote the efflux of excess cholesterol via the cholesterol transporters, ATP-binding cassette transporter A1 (ABCA1). Brain Amyloid-beta elimination across the BBB is modulate by the natural chaperones A-I and ABCA1 is important in Alzheimer's disease (AD). Also, the function and structure of HDL and A-1 were modified inflammation. The aim of the study to clarify the role of HDL and inflammation in mild cognitive impairment (MCI) and AD.
METHODS:
Cross sectional study included 37 AD, 25 MCI, and 75 control without cognitive impairment from database of Study of Outcome and aPolipoproteins in Dementia (STOP-Dementia) registry. The diagnosis of AD and MCI was performed using Brain SPECT : easy Z score Imaging System (e-ZIS; ^{99m}Tc-ECD Fujifilm RI Pharmacy, Tokyo, Japan) by expert neurologists according to Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) criteria by reference some neuropsychological tests (HDSR, MMSE, FAB, CDR, RCPM). Serum HDL subfractions were measured with the electrophoretic separation of lipoproteins employing the Lipoprint system. Neutrophil-lymphocyte ratio (NLR), which is a marker that indicates the peripheral inflammation, was calculated by dividing neutrophil count to lymphocyte count. ApoE genotypes were determined using ABI PRISM 7300 analyzer.
RESULTS:
The score of MMSE and HDSR were 19.6±5.0, 19.1±4.5 for AD, 25.5±2.9, 23.4±4.7 for MCI and 29.4±1.6, 29.4±1.5 for control group. The score of severity and extent of brain SPECT e-ZIS

were 1.54±0.76, 25.0±21.0% for AD and 0.84±0.37, 5.4±7.1% for MCI. Compared whit control group, MCI group had significantly higher BUN, TC, LDL-C, and NLR. Furthermore, compared with control group, AD group had higher LDH and NLR. NLR was negatively correlated with HDS-R and MMSE score (r=-0.389 and -0.273, respectively). MCI group had significantly greater small sized HDL particles than control group. There was no difference in total HDL-cholesterol levels among three groups. The allele frequency for epsilon 4 allele carrier was 63.2, 69.2 and 19.6% in AD, MCI and control subjects, respectively. The odds ratio (OR) of epsilon 4 allele for AD and MCI was 3.2 and 3.5, respectively.
CONCLUSION:
These findings suggest that the quality of HDL and inflammation might be associated with the development of AD.

Disclosures: R. Ohtani: None. **S. Nirengi:** None. **K. Tsuzaki:** None. **K. Kotani:** None. **N. Murase:** None. **M. Sainouchi:** None. **Y. Kuwata:** None. **M. Tatata:** None. **Y. Masuda:** None. **M. Nakamura:** None. **N. Sakane:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.16/M6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Retrotope Inc

Title: A new treatment paradigm for neurodegeneration: isotope-reinforced polyunsaturated fatty acids mitigate cognitive impairment in a mouse model of sporadic alzheimer’s disease

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Abstract: Polyunsaturated fatty acids (PUFAs) are essential nutrients that have to be supplied through the diet, and which are then incorporated into lipid structures throughout the body. Lipid peroxidation (LPO) of PUFAs is detrimental to cells, and toxic aldehyde markers of LPO, e.g. 4-hydroxynonenal (HNE) are elevated in several neurodegenerative diseases, including Alzheimer’s disease (AD). To stabilize but minimally change critical PUFAs, incorporation of deuterium at bis-allylic positions (D-PUFAs) utilizes the ‘kinetic isotope effect’ to inhibit the initiation phase of LPO. We assessed the effects of a D-PUFA-enriched diet in an oxidative stress-based mouse model of cognitive impairment based on gene deletion of aldehyde

dehydrogenase 2 (ALDH2). ALDH2 is important for the detoxification of endogenous aldehydes such as HNE, and Aldh2-/- mice exhibit oxidative stress, a progressive decline in recognition and spatial memory, anxiety-like behavioural changes, and a number of AD-like pathological changes. Multiple cognitive function tests demonstrated mitigation of cognitive impairment in Aldh2-/- mice fed a D-PUFA diet to a level of cognitive performance similar to wildtype mice, whereas no such changes occurred in Aldh2-/- mice fed the control (H-PUFA) diet. In addition, the D-PUFA diet markedly reduced the levels of lipid peroxidation markers (F2-isoprostanes) in cortex and hippocampus. These data, coupled with early signs of efficacy in a recent Phase I/II clinical trial of D-PUFAs for the treatment of Friedreich's ataxia (a rare neuromuscular disorder characterized by excessive mitochondrial LPO) suggest D-PUFAs represent a promising new strategy to prevent cellular damage due to oxidative stress-induce LPO in a broad range of pathological conditions.

Disclosures: **A. Elharram:** 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.; Retrotope Inc. **N. Czegledy:** 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.; Retrotope Inc. **M. Golod:** 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.; Retrotope Inc. **G.L. Milne:** 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.; Retrotope Inc. **E. Pollock:** 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.; Retrotope Inc. **M.S. Shchepinov:** A. Employment/Salary (full or part-time):; Retrotope Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Retrotope Inc. **B. Bennett:** 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.; Retrotope Inc.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.17/M7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DZNE

MPG

K. Hardt Foundation

Title: Antibody-mediated inhibition of Tau aggregation *In vitro*, in neuronal cell models, and in transgenic mice

Authors: *S. KANIYAPPAN[1,2], R. R. CHANDUPATLA[1,2], R. FEEDERLE[3], E. KREMMER[3], E. MANDELKOW[1,2,4], E. M. MANDELKOW[1,2,4]
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Abstract: The repeat domain of Tau protein with the pro-aggregant mutation ΔK280 (TauRD-ΔK280) induces toxicity in transgenic mice and organotypic hippocampal slice culture models (Sydow et al., JN 2011, Messing et al., NBA 2013). Oligomeric forms of TauRD-ΔK280 indeed cause severe synaptotoxicity (Kaniyappan S et al., 2017, Alz&Dem, in press). One of the strategies to prevent such toxic effects is to inhibit the aggregation of Tau or neutralize the toxicity by antibodies. We generated monoclonal antibodies against purified low-n oligomers of TauRD-ΔK280, revealing antibody affinities in the μM to nM range. Several antibodies were used to check their ability to inhibit the aggregation of Tau in vitro by biophysical and microscopic methods. Two antibodies had the ability to inhibit the aggregation of hT40-P301L Tau in in vitro analyzed by ThS and DLS. Structural analysis by AFM revealed that Tau fibrils or higher aggregates were absent in the presence of these antibodies. A split-luciferase complementation assay in N2a cells revealed that Tau aggregation was inhibited if the antibodies were applied extracellularly at an early stage. By confocal microscopy we observed that antibodies were internalized into N2a cells and co-localized with lysosomes. Treatment of Tau-transgenic mice (mutations ΔK280 or P301L) with antibodies are underway.

Disclosures: **S. Kaniyappan:** 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.; DZNE, MPG, and Tau Consortium. **R.R. Chandupatla:** None. **R. Feederle:** None. **E. Kremmer:** None. **E. Mandelkow:** None. **E.M. Mandelkow:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.18/M8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Extra virgin olive oil diet attenuates amyloid and tau pathology and improves cognitive function in alzheimer's disease mice

Authors: *E. LAURETTI[1], L. IULIANO[2], D. PRATICO'[1]
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Abstract: Several epidemiological studies have suggested that the Mediterranean diet protects the brain from the detrimental effect of aging and that extra virgin olive oil, its principal component, may help to reduce the risk of developing Alzheimer's disease and other forms of dementia. However, the mechanisms involved in this protective action is still incompletely understood. The aim of the present study was to investigate whether daily consumption of extra-virgin olive oil enriched diet (EVOO) could modulate amyloid and tau pathology and improve cognitive function in the 3xTg mice. To accomplish this goal, 6 month-old 3xTg mice received either regular chow or chow diet supplemented with EVOO for 6 months.
At the end of the treatment, compared with controls, mice receiving the EVOO-rich diet had an amelioration of their behavioral deficits, and a significant increase in the steady state levels of synaptophysin, a protein marker of synaptic integrity. In addition, they had a significant reduction in insoluble Aβ peptide levels and deposition, lower amount of phosphorylated tau protein at specific epitopes, which were secondary to an activation of the cell autophagic machinery.
Taken together, our findings support a beneficial effect of EVOO consumption on all major features of the AD phenotype (behavioral deficits, synaptic pathology, Aβ and tau neuropathology), and demonstrate that autophagy activation is the mechanism underlying this biological action.

Disclosures: E. Lauretti: None. **L. Iuliano:** None. **D. Pratico':** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.19/M9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R01AG050253

R01AT007411

R21AG049477

Title: LISPRO, an ionic cocrystal of lithium, mitigates Alzheimer-like pathological changes in the mice

Authors: A. HABIB[1], D. SAWMILLER[1], S. LI[1], Y. XIANG[1], D. RONGO[1], J. TIAN[1], H. HOU[1], J. ZENG[1], A. SMITH[2], S. FAN[1], B. GIUNTA[1], T. MORI[4], G. CURRIER[1], D. R. SHYTLE[2], *J. TAN[3]
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Abstract: Lithium has been used for a long time as a mood stabilizer for bipolar disorder as well as for treatment of mania, depression and suicidal thoughts. In addition, recent studies indicates that lithium can prevent cognitive decline associated with Alzheimer's disease (AD). However, one of the main problems that exist in the currently FDA-approved lithium pharmaceutics (carbonate and citrate) is that it has narrow therapeutic index and lithium plasma level change drastically which can cause adverse side effects. Here we investigated the safety, pharmacokinetics and therapeutic efficacies of LISPRO (ionic co-crystals of lithium salicylate with organic l-proline), lithium salicylate and Li_2CO_3. We found that LISPRO reduces β-amyloid plaques and phosphorylation of tau through modulation of inflammation and GSK3β inactivation in the AD mice. Specifically, cytokine profiles in the brain, plasma and splenocyte suggest that LISPRO (8-weeks) down-regulates pro-inflammatory, up-regulates anti-inflammatory and suppresses renal COX2 expression in Tg2576 mice. Plasma and brain pharmacokinetics of lithium indicated that LISPRO showed significantly higher brain and steady plasma lithium levels on B6129F2/J (2 weeks) and Tg2576 (8 weeks) mice. Interestingly, chronic administration of LISPRO for 28 weeks produces a slightly higher, but non-significant brain to plasma lithium levels and reduces β-amyloid plaques, and tau-phosphorylation through modulation of presynaptic (synaptophysin) and post-synaptic protein (PSD95) expression in 3XTg-AD mice.

Disclosures: **A. Habib:** None. **D. Sawmiller:** None. **S. Li:** None. **Y. Xiang:** None. **D. Rongo:** None. **J. Tian:** None. **H. Hou:** None. **J. Zeng:** None. **A. Smith:** None. **S. Fan:** None. **B. Giunta:** None. **T. Mori:** None. **G. Currier:** None. **D.R. Shytle:** None. **J. Tan:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.20/M10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: UCI FRT

ICTS UL1 TR001414

Title: Levetiracetam prevents age-related cognitive impairment in a sex-specific manner in mice lacking synaptic zinc

Authors: *M. MAHAVONGTRAKUL[1], E. VOGLER[1], A. TRAN[1], R. NAMEKI[2], C. CHINN[1], C. COX[1], J. BUSCIGLIO[1]
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Abstract: While it has been known for a while that patients with Alzheimer's Disease (AD) have increased risk of unprovoked seizures, only recently has hyperexcitability become a major focus of AD research. Increased hippocampal activity in patients with mild cognitive impairment (MCI) was initially thought to be a beneficial compensatory mechanism; however, recent research has shown that patients with MCI who are treated with antiepileptic drugs improved their cognition. Synaptic zinc, co-released with Aβ during neurotransmission, is implicated in both oligomer formation and modulation of excitatory neurotransmission. Synaptic zinc is packaged into synaptic vesicles by ZnT3; thus, ZnT3KO mice lack synaptically-released zinc. These mice exhibit increased susceptibility to seizures and synaptic dysfunction, consistent with the finding that synaptic zinc is sequestered by Aβ oligomers. In fact, ZnT3KO mice exhibit age-dependent increases in markers of seizure activity, synaptic loss, neurodegeneration, strikingly similar to that in AD mouse models. Although ZnT3KO mice do not exhibit spontaneous convulsive seizures, our data suggests that these mice exhibit epileptiform activity. In addition, we have recently shown that chronic, but not acute, treatment with the antiepileptic drug Levetiracetam (LEV) prevents cognitive decline in these mice, suggesting a mechanism of action independent of antiseizure activity. In this regard, the mechanism by which LEV prevents cognitive decline is not understood. The goal of this project was to begin characterizing gene networks involved in the mechanism of action of LEV leading to the prevention of cognitive decline in the ZnT3KO mouse model. mRNA was extracted from 6-month-old ZnT3KO mice and analyzed using Nanostring. Gene analysis indicated sex-specific changes genes involved in epigenetics, neurogenesis, and hyperexcitability. To investigate the effects of chronic LEV on neurogenesis important for learning and memory, ZnT3KO mice were fed bromodeoxyuridine and immunohistochemistry was performed on brain sections. Although there was an increase in neurogenesis in LEV-treated animals, this increase was restricted to females, further suggesting a sex-specific effect of LEV. Lastly, ZnT3KO mice were implanted with surface electroencephalogram (EEG) electrodes and the results suggest abnormal EEG activity in aged ZnT3KO mice. Taken together, these results suggest that LEV prevents cognitive impairment in ZnT3KO mice in a sex-specific manner at multiple layers of regulation, including epigenetics, neurogenesis, and hyperexcitability.

Disclosures: M. Mahavongtrakul: None. **E. Vogler:** None. **A. Tran:** None. **R. Nameki:** None. **C. Chinn:** None. **C. Cox:** None. **J. Busciglio:** None.

Poster

127. Preclinical Therapeutic Strategies for Neurodegenerative Disease I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 127.21/N1

Topic: I.05. Biomarker and Drug Discovery

Support: National Key Basic Research Program of China (2013CB530900)

the Research Grants Council, HKSAR (HKUST 12/CRF/13G and GRF660813)

Hong Kong PhD Fellowship Scheme

Title: Using ATM deficiency as a model for drug discovery with application to neurodegenerative disease

Authors: *B. ZHU, K. HERRUP
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Abstract: There is a great need to identify new drugs that retard the progress of late onset neurodegenerative diseases such as Alzheimer's disease (AD) and delay their age of onset. Unfortunately, it generally takes a long time to test a drug's effect *in vivo*. Previously, our lab has shown that the ATM kinase is involved in the degeneration of neurons, in mice and in humans, during the AD disease process (Shen et al., 2016). *Atm* is the gene that is mutated in ataxia-telangiectasia (A-T), a childhood neurodegenerative disease, showing features of early aging. Here, we propose to use the ATM-deficient mice as an *in vivo* model for discovering drugs with neuroprotective properties that would be useful in diseases such as AD.
In A-T, a significant loss of cerebellar granule and Purkinje cells occurs, accompanied by the loss of neuronal cell cycle control. This occurs between postnatal day 10 (P10) and P20 in the Purkinje cells (Yang and Herrup, 2005). This narrow time window of the cell cycle re-entry allows us to conduct a quick and efficient test for neuroprotective drugs.
The flesh extract from New Zealand green lipped mussel (PCSO-524®) has an anti-inflammatory effect and is used as a supplement to treat arthritis. We have found that PCSO-524® showed anti-aging effect *in vitro*, decreasing both neuronal cell cycle reentry and cellular senescence. PCSO-524® also shows protection against the effects of KU 55933, an ATM specific inhibitor. In order to test PCSO-524®'s effect in vivo, we gave ATM-deficient mice oral doses for three weeks beginning at P10. Following the final dose, the mice were sacrificed and their brains prepared for immunostaining. We found that in the ATM deficient mice, the PCNA and Ki67 were significantly blocked by the PCSO-524® compared with vehicle control. This demonstrates the effectiveness of the PCSO-524® and also validates the use of ATM-deficient mice for rapid drug screening for compounds with protective potential against neurodegenerative disease. We believe that this model has the potential to accelerate the process of drug discovery.

Disclosures: **B. Zhu:** None. **K. Herrup:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.01/N2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG043503

NIH Grant AG17856

Dana Foundation

Title: Functional imaging signatures of pathological spread across TDP-43 proteinopathies

Authors: *P. M. FERRARO[1,3], C. A. JESTER, III[1], C. A. OLM[1,2], K. PLACEK[1], F. AGOSTA[3], L. ELMAN[1], L. MCCLUSKEY[1], D. J. IRWIN[1], M. FILIPPI[3], M. GROSSMAN[1], C. MCMILLAN[1]
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Abstract: TAR DNA-binding protein 43 (TDP-43) pathological inclusions can result in pure motor (ALS-motor), pure behavioural (bvFTD) or a combination of motor and behavioural (ALS-FTD) impairments. However, TDP-43 mediated degeneration propagates through the brain differentially across these syndromes. Cerebral blood flow (CBF) may provide an early marker of potential impending damage and/or compensatory alterations that precede evidence of TDP-43 associated grey matter (GM) loss. The objective of the present work was to evaluate proxies for pathological spread in various TDP-43 proteinopathies using GM atrophy and CBF measurements. We evaluated ALS-motor (N=14), bvFTD with either a neuropathological diagnosis and/or a known genetic mutation associated with FTLD-TDP pathology (N=11), ALS-FTD (N=13) patients and healthy controls (N=33) who completed T1-weighted and pseudo-continuous arterial spin labeling (pCASL) Magnetic Resonance Imaging (MRI). Data were processed using dedicated pipelines in Advanced Normalization Tools (ANTs) to compute cortical thickness (CT) and partial volume-corrected CBF. Relative to controls, bvFTD patients showed marked atrophy of the prefrontal and temporal cortices, hypoperfusion encompassing orbitofrontal regions and hyperperfusion in primary motor areas. ALS-FTD cases exhibited significant temporal atrophy, widespread orbitofrontal hypoperfusion as well as distinct areas of increased and decreased perfusion in primary motor regions. ALS-motor patients showed no significant GM atrophy but evident hypoperfusion encompassing primary motor regions. Direct comparisons between patient groups revealed hypoperfusion in motor and orbitofrontal regions

in ALS-FTD relative to ALS-motor and bvFTD patients, respectively. Hyperperfusion in motor regions suggests compensatory responses to incipient underlying pathology in bvFTD phenotypes. Greater motor and orbitofrontal hypoperfusion in ALS-FTD may be related to TDP-43 burden in critical regions associated with these diseases. Hypoperfusion in motor areas in ALS-motor cases suggests that perfusion alterations can provide an early marker of pathological spread and impending decline even in diseases lacking significant brain structural damage. In conclusion, hypoperfusion was associated with clinically manifest regions of degeneration while hyperperfusion was observed in clinically silent areas, suggesting that perfusion changes may mark specific vulnerable brain hubs and inform on trajectories of neurodegeneration across TDP-43 proteinopathies.

Disclosures: P.M. Ferraro: None. **C.A. Jester:** None. **C.A. Olm:** None. **K. Placek:** None. **F. Agosta:** None. **L. Elman:** None. **L. McCluskey:** None. **D.J. Irwin:** None. **M. Filippi:** None. **M. Grossman:** None. **C. McMillan:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

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Program#/Poster#: 128.02/N3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 5R21AG041472-02

DOD Grant W81XWH-14-1-0467

Title: Diagnostic and therapeutic potential of antibody fragments selective for human AD brain derived tau variants

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Abstract: Protein aggregation is a common feature in many neurodegenerative diseases. Small oligomeric protein variants including tau, prions & alpha-synuclein, have been implicated in the pathogenesis & spread of disease. Reagents that can selectively recognize specific tau variants associated with onset & progression of Alzheimer’s disease (AD) & other tauopathies can be effective diagnostic & therapeutic tools.Tau is important in the assembly & maintenance of microtubule stability in healthy neurons. In AD, hyperphosphorylation or tau interferes with microtubule assembly affecting axonal transport. We utilized a novel atomic force microscopy (AFM) based biopanning protocol to isolate around 60 single chain variable fragment (scFvs)

that selectively bind tau variants present in human AD but not cognitively normal age matched brain tissue. The scFvs were screened with pooled tissue from post-mortem human brain tissue either from the mid temporal gyrus (MTG) of 2 early stage AD (Braak stage III), 7 late stage AD (Braak stage V), or 2 healthy age matched controls. As expected none of the selected scFvs had substantial binding to the healthy control tissue. However, the scFvs did show differential binding to AD Braak stage III & V homogenates indicating that different tau variants are generated during different stages of AD. Since the scFvs binding early AD stages may have value as early biomarkers of AD, we also analyzed sera samples from human post-mortem AD & control cases. The scFvs readily selected the AD samples over the controls indicating that these tau variants are present in blood & may also serve as therapeutic targets. Therapeutic benefit of these scFvs in invitro assay have also been indicated.

Disclosures: L. Venkataraman: None. **P. He:** None. **T.G. Beach:** None. **C. Peltz:** None. **K. Yaffe:** None. **M.R. Sierks:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH grant AG037376

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NIH grant AG017586

NIH grant NS053488

NIH grant AG038490

NIH grant AG052943

Title: Quantifying effects of Alzheimer's disease on the human hippocampus using an *Ex vivo* atlas combining MRI and histology

Authors: *L. WISSE[1], D. ADLER[1], R. ITTYERAH[1], J. B. PLUTA[1], S.-L. DING[5], L. XIE[1], J. WANG[1], S. KADIVAR[1], J. L. ROBINSON[1], T. SCHUCK[1], J. Q. TROJANOWSKI[2], M. GROSSMAN[3], J. A. DETRE[1], M. A. ELLIOTT[1], J. B. TOLEDO[1], W. LIU[1], S. PICKUP[1], S. R. DAS[4], D. A. WOLK[1], P. A. YUSHKEVICH[1]
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Abstract: Background: There has been increasing interest in detailed hippocampal subfield morphometry in cognition, aging and disease research using in vivo MRI. However, research on in vivo morphometry is hampered by lack of a definitive reference model describing regional effects of aging and disease pathology on the hippocampus. Histological studies (e.g. Rossler et al, Acta Neuropathol, 2002; Simic et al., JOCN, 1997) provide limited reference information due to their 2D nature, use of a measure like cell count rather than volume or thickness, and inconsistency between studies. We therefore built a 3D probabilistic atlas of the hippocampus combining post-mortem MRI with histology to serve as a reference for in vivo morphometry and to investigate hippocampal anatomy in Alzheimer's disease (AD). **Methods:** 0.2x0.2x0.2 mm^3 9.4T MR images from 31 ex vivo hippocampal specimens (13 normal controls (NC), 18 cases with a clinical diagnosis of dementia; of which 9 AD; mean age at death: 75 years) and histological sections with Kluver-Barrera staining at 0.2 mm intervals from 9 of the 31 specimens were combined into a probabilistic atlas of the hippocampus (Fig. 1a). **Results:** All subfields were significantly smaller in AD compared to NC after age correction, with the largest decrease of ~40% in CA1 and stratum radiatum lacunosum moleculare (SRLM). The DG/CA1 ratio was significantly larger in AD than CN, indicating that CA1 is more affected than DG in AD. T-statistic maps (Fig. 1b) reveal that SRLM is affected throughout its length, but show localized effects in the grey matter in middle/posterior regions. **Discussion:** This probabilistic post-mortem atlas of the hippocampus allowed us for the first time to investigate AD-related effects on hippocampal subfield morphometry, derived from histology, in 3D. These results support the hypothesis of differential involvement of hippocampal subfields in AD, providing further impetus for studying hippocampal subfields in relation to aging, disease and cognition during life. In addition, this atlas can serve as a reference for in vivo subfield research.

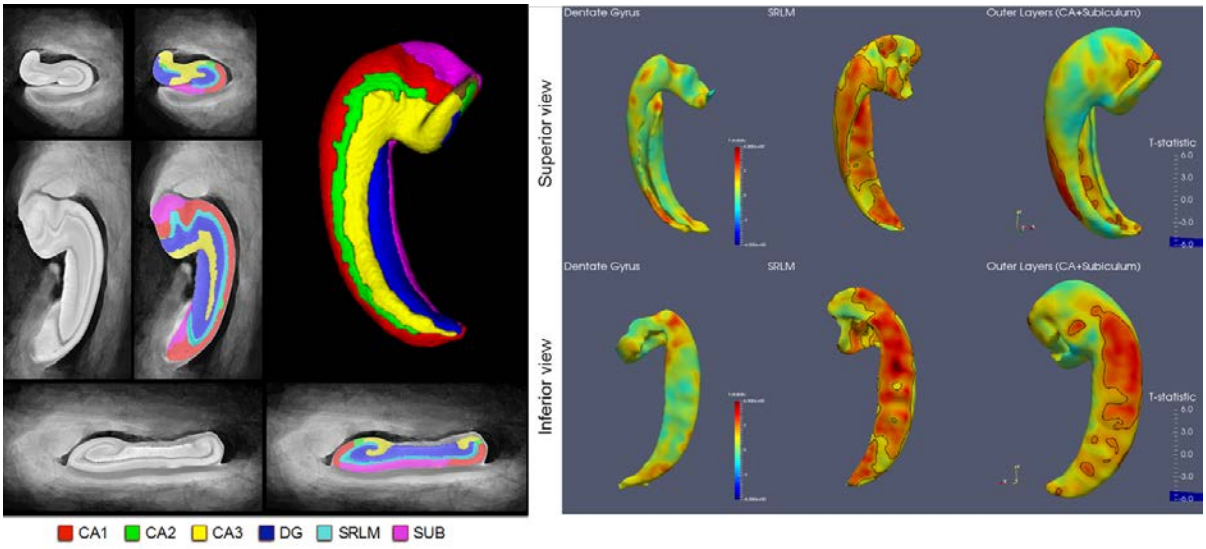

Figure 1a. Distribution of histologically-derived hippocampal subfields in the ex vivo atlas template; 1b. T-Statistics map of the NC-AD effect on the thickness of the dentate gyrus, stratum radiatum lacunosum moleculare (SRLM) and outer layers. Black curves outline the clusters that are statistically significant using an FDR threshold of 0.05

Disclosures: L. Wisse: None. **D. Adler:** None. **R. Ittyerah:** None. **J.B. Pluta:** None. **S. Ding:** None. **L. Xie:** None. **J. Wang:** None. **S. Kadivar:** None. **J.L. Robinson:** None. **T. Schuck:** None. **J.Q. Trojanowski:** None. **M. Grossman:** None. **J.A. Detre:** None. **M.A. Elliott:** None.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.04/N5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Intramural research program

Title: Extracellular vesicle biomarkers predict response to intranasal insulin treatment in Alzheimer's disease

Authors: *M. MUSTAPIC[1], J. TRAN[1], S. GULYANI[1], S. CRAFT[2], D. KAPOGIANNIS[1]
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Abstract: Insulin resistance (IR) and changes in the insulin signaling pathway have been implicated in Alzheimer’s disease (AD) pathogenesis. Intranasal insulin has been proposed as a treatment strategy for overcoming brain IR in AD. We previously detected IR-related markers in extracellular vesicles (EVs) enriched for neuronal origin including pSer312-IRS-1, pan-pY-IRS-1, and targets downstream in the pathway (phosphorylated AKT, GSK3β and S6RP). In the present study, we analyzed samples from the double-blind placebo-controlled clinical trial of intranasal insulin (Study of Nasal Insulin to Fight Forgetfulness (SNIFF)) to assess whether candidate biomarkers from neuronal-enriched EVs change following intranasal insulin treatment and predict cognitive change evaluated by ADAS-cog.
We isolated EVs from 91 participants, pre-and post 4-month treatment with placebo [N=26], or 20 IU insulin [N=33], or 40 IU insulin [N=32]), and analyzed differences taking into account sex (male, female), and APOE genotype (APOEe4 carrier [e4+] or non-carrier[e4-]). Insulin-induced changes in pSer312-IRS-1 were modulated by APOE and sex ($p<0.05$). Treatment with 20 IU insulin decreased pSer312-IRS-1 in e4+ subjects, but increased it in e4- subjects compared to placebo. The same dose increased phosphorylated GSK3β in e4- treated subjects compared to placebo ($p<0.03$). Treatment with 40 IU insulin decreased pSer312-IRS-1 compared to placebo in e4+ men ($p<0.05$), but increased it in e4+ women ($p<0.04$). Levels of phosphorylated S6RP decreased in response to 20 or 40 IU insulin in e4- subjects compared to placebo.
To determine whether changes in EV markers in response to treatment were related to clinical changes we used Spearman correlations. For both male APOE groups and the APOEe4- women treated with 20 IU insulin, decreased pSer312-IRS-1 was associated with improved (decreased) ADAS-Cog scores (rho=0.75 and 0.51, ps<0.001 and 0.02).
In a subgroup of participants who underwent FDG-PET, regional changes in CMRglu following

insulin treatment were correlated with changes in EV markers.
We have shown that intranasal insulin induces different patterns of change in EV biomarkers depending on treatment dosage, ApoE genotype, and sex. The validity of EV biomarker changes is further strengthened by their relation to cognitive performance. This research was supported entirely by the Intramural Research Program of the NIH, National institute on Aging.

Disclosures: M. Mustapic: None. **J. Tran:** None. **S. Gulyani:** None. **S. Craft:** None. **D. Kapogiannis:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.05/N6

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: B-lymphocytes imbalances of PKCe and cellular aggregation in Alzheimer's disease patients

Authors: *F. V. CHIRILA, J. WALLACE, W. MACTURK, G. XU, D. ALKON
NeuroDiagnostics LLC, Rockville, MD

Abstract: The inaccuracy of the diagnosis for Alzheimer's disease (AD) has made the therapeutic intervention difficult, particularly early enough to prevent significant neurodegeneration and cognitive dysfunction. Here, we describe a novel, highly accurate peripheral diagnostic for AD patients based on quantitatively measured PKCε and aggregation rate of human immortalized B-lymphocytes. The low levels of PKCε and the elevated aggregation rate with increasing cell density in AD cases is the basis of the new bio-markers. The PKCε level in Alzheimer disease patients is the lowest compared with the other two groups of patients,Non-Alzheimer’s Disease Demented (Non-ADD) and Age-matched Control (AC). This result is analogous to the PKCε effect seen in skin fibroblasts and brain. The total protein concentration for B-lymphocytes correlates linearly with the cell density (Pearson’s linear correlation coefficient 0.916). The PKCε levels in the AD cases is lower than the Non-ADD cases with a statistical significance of $P<0.001$. When doubling the seeding cell seeding density, on Matrigel, from 125 cells/µl to 250 cells/µl the % Aggregate Area for the Alzheimer’s disease cases (AD) is elevated when compared with Non-Alzheimer’s Demented (Non-ADD) or Age-matched Control (AC) cases. The slope, representing the Aggregation Rate, is approximately 10-fold higher in the AD cases when compared with the AC and Non-ADD cases. This result is analogous to the Aggregation Rate effect seen in skin fibroblasts. The new bio-markers, were successfully cross-validated on the same cell lines, and showed a complete overlap. Based on the high accuracy of this strategy, the bio-marker profile appears to identify accurately the AD patients for therapeutic intervention.

Disclosures: **F.V. Chirila:** A. Employment/Salary (full or part-time):; NeuroDiagnostics LLC. **J. Wallace:** A. Employment/Salary (full or part-time):; NeuroDiagnostics LLC. **W. MacTurk:** A. Employment/Salary (full or part-time):; NeuroDiagnostics LLC. **G. Xu:** A. Employment/Salary (full or part-time):; NeuroDiagnostics LLC. **D. Alkon:** A. Employment/Salary (full or part-time):; NeuroDiagnostics LLC.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.06/N7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: R37AG036800

RO1AG052258

RO1AG049711

McKnight Brain Research Foundation

Title: Circulating exosomal miRNA as a biomarker for age-related cognitive decline and decreased hippocampal volume

Authors: *A. RANI[1], A. O'SHEA[2], L. IANOV[3], R. COHEN[2], A. J. WOODS[4], T. C. FOSTER[5]
[1]Univ. of Florida Med. Col., Gainesville, FL; [2]Genet. and Genomics Program, Genet. Institute,, Gainesville, FL; [3]Evelyn F. and William L. McKnight Brain Inst., [4]Clin. and Hlth. Psychology, Univ. of Florida, Gainesville, FL; [5]Dept Neurosci., Evelyn F. and William L. McKnight Brain Inst. Univ. Florida, Gainesville, FL

Abstract: Neuroimaging, genetics, and circulating biomarkers are being developed to differentiate normal aging from diseases that affect cognition. The blood-based biomarkers could provide a simple non-invasive and relatively inexpensive means for tracking the progression of cognitive decline and effectiveness of treatments, as well as providing information on mechanism for cognitive impairment. For example, circulating levels of microRNAs (miRNAs) may be able to identify individuals with Alzheimer’s disease. We describe plasma exosomal fraction miRNA as possible biomarkers of cognitive decline during normal aging. Cognitive function (MoCA) was characterized for males (n = 54) and females (n = 76) (age range 44-102 years, average 73 years). Exclusionary criteria included pre-existing neurological/psychiatric disorders, MRI exclusions, mild cognitive impairment (MoCA<20) or diagnosis with a neurodegenerative disease. The plasma exosome fraction was isolated and the expression of miRNA was examined using next generation sequencing. The results for miRNA expression confirmed previous research, which characterized the overall pattern of expression of miRNA in

plasma, differential expression of select miRNA for males and females, and a relationship between miRNA expression and age. In order to examine the relationship of miRNA expression and cognitive function, factor analysis was used to remove the confounding influence of age and sex and limit the number of miRNA examined. Eight factors described 82% of the variability in miRNA expression. The top 10 miRNA for each factor were examined using multiple regress to determine if the expression correlated with age, cognitive measures, or differed across sex. One factor was enriched miRNA that correlated with cognition (5 out of 10). The five cognition-related miRNA did not vary according to age or sex and the pattern of expression for cognition-related miRNA did not match that previously described for Alzheimer's disease indicating that these are markers of normal age-related cognitive decline. Cognitive-related miRNA are relatively enriched in the brain. In contrast, we observed that expression in circulation was relatively low and expression increased as cognitive function declined. Finally, pathway analysis indicated possible links to brain function. The results suggests that impaired cognition may be associated with increased synthesis and/or release of miRNA from the brain.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.07/N8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Functional biomarker of rare and familiar diseases: NPC1 knockout neuronal networks phenotyped with HTS micro electrode arrays and artificial intelligence machine learning methods

Authors: *X. FENG[1], B. M. BADER[2]
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Abstract: There is an urgent need to develop fast and reliable disease models in rare diseases which can be used for screening in a standardized manner. One strategy is the development of more predictive pre-clinical in vitro model for gene-associated diseases such as Niemann-Pick Disease TypC1. Niemann-Pick Type C disease (NPC) is an autosomal recessive neurodegenerative disease caused by a mutation in either the NPC1 gene (in 95% of cases) or the NPC2 gene (in 5%). The pathological changes in NPC1 are characterized by the excessive storage of unesterified cholesterol in lysosomes. NPC Patients show increasing loss of motor control, seizures and other neuropathological symptoms. Using a cell cultures from NPC1 knockout mice, we aimed to identify a correlation between the disease-associated genotype and

its functional in vitro phenotype. We cultured homozygous knockout and wildtype NPC1 neuronal networks on HTS-compatible multiwell micro-electrode arrays (MEA) for at least four weeks to analyze their functional electrophysiological activity patterns quantified by multi-parametric analysis. We show that NPC1 knockout cell culture exhibit a significantly different functional phenotype shown by different activity levels and neuronal communication. Moreover, the functional development into mature neuronal networks is affected by the knockout of the NPC1 gene. In conclusion, we present a means to functionally phenotype gene-associated disease in vitro models by machine learning methods and thus provide functional biomarkers for screening small molecules or natural compounds potentially rescuing these functional phenotypes.

Disclosures: X. Feng: None. **B.M. Bader:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIA Grant 1R56AG053961

Title: Fitness and lifestyle affect neural and cognitive risk factors for Alzheimer's Disease in older African Americans

Authors: *N. SINHA[1], M. A. GLUCK[2]
[1]Ctr. for Mol. and Behavioral Neurosci., Rutgers, Newark, NJ; [2]Rutgers Univ. Newark, Newark, NJ

Abstract: African Americans are at elevated risk for age-related cognitive decline and memory loss, having double the prevalence of Alzheimer’s disease (AD) compared to that of white Americans. Stress, sleep deprivation, sedentary lifestyles, poor cardiovascular fitness, depressive symptoms, high body mass, and low education are all known risk factors for cognitive decline and AD; their widespread presence among African Americans, particularly in low socioeconomic groups, has been well documented in previous epidemiological studies. However, little is known about the relative importance of and the interactions between these risk factors, specifically within the African-American communities.
In this study, we address this gap in our understanding of health disparities in Alzheimer’s Disease (AD), by examining the cognitive, neural, and health/lifestyle factors associated with cognitive decline in older African Americans (aged 65 and above). All participants receive a full health, lifestyle, neuropsychological, and cognitive battery; half of those enrolled also participate in brain imaging which involves structural, resting-state and diffusion tensor MRIs.

Here, we present preliminary behavioral and imaging results, which suggest positive relationships between health, fitness and lifestyle factors, and, cognitive function, neural structure, and functional connectivity of regions in the Medial Temporal Lobe (MTL), particularly the Hippocampus/Entorhinal Cortex, which are the earliest known locus of AD pathology. Our results further indicate that intra-MTL connectivity and structural integrity are the intermediary mechanisms through which these risk factors affect cognition.

Disclosures: N. Sinha: None. **M.A. Gluck:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

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Program#/Poster#: 128.09/N10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CNRS Liban

Allenbach Suisse

Title: Proteomics identification of oxidized brain proteins in early stages of neurodegeneration

Authors: *Z. EL HAJJ, M. FOURNIER, I. RIEDERER, K. Q. DO, B. RIEDERER
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Abstract: Background:
Today, Alzheimer’s disease (AD) is one of the most important age-related neurodegenerative diseases and of increasing prevalence. The causes of AD are not well understood. Several hypotheses have been proposed to explain its pathogenesis, including oxidative stress which is increased with aging. In the present project, we investigated two forms of protein oxidation: protein carbonylation and cysteine residues oxidation in the frontal cortex tissues of AD patients at various stages. In a translational approach, we studied the role of oxidative stress in a mouse model with glutathione (GSH) deficit.
Methods:
Carbonylated proteins and oxidized cysteine residues were detected in the frontal cortex of 6 controls, 6 mild AD and 5 severe AD post-mortem samples using the carbonyl labeling and maleimide labeling, repectively, followed by Western blots, 2D gels analyses and protein identification by mass spectrometry. In addition, the effects of GSH deficit on cysteine residues oxidation were investigated in the frontal cortex of genetically impaired GSH synthesis mouse (GCLM-KO, n=4) as compared to wild type (GCLM-WT, n=4).
Results:
In total, ten proteins were found to be affected by carbonylation in mild and/or severe AD

groups. Among of them, T-complex protein 1 (TCP1) and glutamine synthetase were more carbonylated in mild AD. Cysteine residues of twelve proteins were differentially oxidized in mild AD group compared to controls. The affected proteins by both types of oxidation are involved in cytoskeletal structure, glucose metabolism and glial activity. Interestingly, GSH deficit in GCLM-KO mice induced an alteration of same pathways affected in AD in addition to ubiquitin-proteasome system and the increase of peroxiredoxin and thioredoxin oxidation. Glycolysis and cytoskeleton components were more affected by glutathione deficit and in segere AD samples. However, glial proteins were more affected in mild AD.

Conclusions:

Our results highlight an early oxidation of glial proteins in mild AD. Oxidized proteins in CCLM-KO mice reflect the consequences of glutathione deficit in aging and different neurodegenerative pathologies. Oxidative stress is not exclusive for AD and may occur in different brain pathologies in susceptible cells like neurons, glia…. Thus, it is important to define and to determine the alterations due to aging or to the disease in order to better understand the role of oxidative stress in the progression of neurodegenerative diseases.

Disclosures: Z. El HAJJ: None. **M. Fournier:** None. **I. Riederer:** None. **K.Q. Do:** None. **B. Riederer:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.10/N11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Intramural research Program

Title: Extracellular vesicle biomarkers in Alzheimer's disease, mild cognitive impairment, and non-cognitively impaired older adults

Authors: *J. TRAN[1], M. MUSTAPIC[2], B. B. BENDLIN[3], D. KAPOGIANNIS[4]
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disease leading to dementia characterized by accumulation of extracellular amyloid beta (Aβ) in plaques and intracellular phosphorylated Tau (pTau) in tangles. Mild cognitive impairment (MCI) (especially with memory loss) frequently represents an early clinical stage of AD. Our Lab has developed a methodology for isolating Extracellular Vesicles (EVs) of neuronal origin from plasma. We have shown that Aβ and pTau in EVs can predict AD diagnosis up to 10 years prior to clinical diagnosis. This study aims to determine if EV biomarkers allow us to also distinguish between

AD and MCI. We blindly isolated neuronal-origin EVs from serum samples from 50 AD, 50 MCI, and 50 age and sex matched non-cognitively impaired participants from the University of Wisconsin's Alzheimer's Disease Research Center. We measured pTau181, Aβ38, Aβ40, Aβ42, and EV marker TSG101 (as a means of sample normalization) using electrochemiluminescence assays. Nanoparticle tracking analysis was also used to determine size and concentration of EVs. Blind analysis revealed that pTau181 and Aβ42 in Group 3 were higher than in Group 1 ($p = 0.004$ and 0.044 respectively), whereas Group 2 had intermediate values. Conclusions will be drawn after the blinding is lifted. This research was supported entirely by the Intramural research Program of the NIH, National institute on Aging.

Disclosures: J. Tran: None. **M. Mustapic:** None. **B.B. Bendlin:** None. **D. Kapogiannis:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant DP5OD019833

Title: Executive dysfunction is associated with cortical amyloid and tau accumulation in preclinical autosomal dominant Alzheimer disease

Authors: *Y. T. QUIROZ[1], D. NORTON[1], E. GUZMAN-VELEZ[1], A. BAENA[2], A. OVALLE[3], D. JIN[1], V. GAVIRIA[1], F. LOPERA[2]
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Abstract: Background: Autosomal dominant Alzheimer's disease (ADAD) offers a unique opportunity to identify some of the earliest cognitive changes in preclinical AD. Traditionally, research has focused on memory deficits as primary early indicators of AD pathology; however, recent research has suggested that changes in executive function might be present even before memory deficits arise. Executive function in preclinical stages of ADAD and its relation with AD pathology has yet to be explored. This study characterized the relationships between executive function, amyloid and tau deposits in the brains of cognitively unimpaired PSEN1 E280A mutation carriers. Methods: Cross-sectional measures of amyloid (Pittsburgh Compund B, PiB) and tau (Flortaucipir,FTP) PET imaging were assessed in 21 PSEN1 E280A kindred members (age range, 28-44 years); nine cognitively unimpaired carriers and twelve age-matched non-carrier family members. Participants also underwent an executive function battery that included the Institute of Cognitive Neurology (INECO) Frontal Screening, the Stroop word-color

test, the Wisconsin Card Sorting test, and verbal fluency tests (e.g. categories and letters). Spearman correlations characterized the associations between cognitive performance, mean cortical PiB DVR levels, and regional FTP SUVR levels, in both groups. Results: In cognitively unimpaired PSEN1 carriers, performance on the INECO battery was correlated with cortical amyloid (r=-0.7602, p=0.017) and regional tau in entorhinal cortex (r=-0.820, p=0.007) and inferior temporal lobe (r=-0.904, p=0.001). Carrier's performance on the Stroop word-color test was associated with regional tau in entorhinal cortex (r=-0.745, p=0.021). Conclusions: Preliminary findings support a relationship between executive dysfunction and amyloid burden and tau accumulation, among cognitively unimpaired mutation carriers from the Colombian kindred with ADAD. Executive function measures might therefore be useful for identifying individuals who are in late preclinical stages of AD; when amyloid and tau pathologies are known to be present. Future studies in larger samples, and also in comparison to older adults at risk for late onset AD, are needed to substantiate these findings and better understand changes in executive function in preclinical ADAD.

Disclosures: Y.T. Quiroz: None. **D. Norton:** None. **E. Guzman-Velez:** None. **A. Baena:** None. **A. Ovalle:** None. **D. Jin:** None. **V. Gaviria:** None. **F. Lopera:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.12/O1

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Expression profiling and gene regulatory analysis of Synaptosomal-associated protein 25, a biomarker for Alzheimer's disease

Authors: *Y. FENG[1], P. WANG[2]
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Abstract: Synaptosomal-associated protein 25-dKA (SNAP-25) is a presynaptic plasma membrane protein which is localized and highly expressed in the nerve terminals. Within the nerve terminals, SNAP-25 is mainly responsible for synaptic vesicle fusion and/or docking as well as neurotransmitter release. Bioinformatics analysis showed that SNAP-25 is down-regulated within patients diagnosed with Alzheimer's Disease (AD) and could serve as a genetic biomarker given its low expression levels. We obtained gene expression data from the Gene Expression Omnibus (GEO) database and identified a combined 1,033 significantly correlated genes based on SNAP-25 through Pearson Correlation Coefficient (PCC). Differentially expressed genes (DEGs) were calculated via GEO2R by comparing AD patients with controls. A total of 1,071 DEGs were identified. We screened for biological pathways using the Database for

Annotation, Visualization, and Integrated Discovery (DAVID) and carried out Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment analyses. Using the 420 Differentially Co-Expressed Genes (DCGs), results showed that the predominately enriched pathways are Parkinson's Disease, Alzheimer's Disease, and Oxidative phosphorylation. In addition, we constructed a regulatory network and found sequence motifs for SNAP-25 using Hypergeometric Optimization of Motif Enrichment (HOMER). In HOMER, 13 significantly enriched transcriptional factor motifs were determined including KLF14, NRF1, Maz, Sp5, Smad2, NRF, REST, CRE, YY1, Smad4, HIF-1b, Zfp281, and SLUG. Our study attempts to further correlate the relationship between SNAP-25 and AD, as well as pathogenesis of other possible neurological disorders.

Disclosures: Y. Feng: None. **P. Wang:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.13/O2

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Neurogranin in human Alzheimer's disease brain is associated with tau

Authors: *Y. DING[1], E. ZHEN[1], C. RUBLE[1], B. GHETTI[2], H. VANDERSTICHELE[3], E. STOOPS[3], J. L. DAGE[1]
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Abstract: Neurogranin is a postsynaptic protein containing 78 amino acids. It is known to accumulate at the dendritic spines of forebrain neurons and to bind to plasma membranes with its IQ motif (A29-K44) (Biochem J. 2007; 404(Pt 1): 31-43). Neurogranin plays multiple roles in the central nervous system. It binds to calmodulin in a Ca^{2+} dependent manner and regulates the calcium-mediated second messenger cascades, as well as synaptic plasticity (J Biol Chem. 1994;269(35):22420-6). As a PKC substrate (J Biol Chem. 1991;266(1):229-37), its phosphorylation status is also found to affect long-term potentiation (Eur J Neurosci. 2011;33(2):244-50). Moreover, recent reports demonstrated that levels of neurogranin and one of its truncated versions are elevated in Alzheimer's disease (AD) and mild cognitive impairment (MCI) patient cerebral spinal fluid (CSF), indicating that neurogranin might serve as a CSF-based biomarker for diagnosis of AD (J Alzheimers Dis. 2016; 53(4): 1523-1538; Alzheimers Dement. 2015 Dec;11(12):1461-9). However, there is limited research describing the etiology of increased levels of neurogranin in AD and no evidence is showing if elevated protein levels are correlated with expression changes of neurogranin in the brain. Thus, we examined and compared the expression profiles of full-length neurogranin and its C-terminal truncated mutant

across several brain regions from subjects that spanned Braak stages of tau pathology, indicating different biological roles of full-length and truncated neurogranin. Additionally, our research confirmed the association between neurogranin and Tau or p-Tau. Together, our research demonstrates novel insights on the etiology of elevated neurogranin in CSF and its role as an Alzheimer's disease biomarker.

Disclosures: **Y. Ding:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **E. Zhen:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **C. Ruble:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **B. Ghetti:** None. **H. Vanderstichele:** A. Employment/Salary (full or part-time):; ADx NeuroSciences NV. **E. Stoops:** A. Employment/Salary (full or part-time):; ADx NeuroSciences NV. **J.L. Dage:** A. Employment/Salary (full or part-time):; Eli Lilly and Company.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.14/O3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Highly sensitive single molecular array immunoassay quantitation of neuronal proteins t-Tau, pTau231, Abeta42, and NF-L in CSF and Alzheimer's disease plasma

Authors: A. CHENNA[1], C. J. PETROPOULOS[1], *J. W. WINSLOW[2]
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Abstract: Altered levels of neuronal proteins associated with damage and/or as candidate prognostic biomarkers of Alzheimer's disease (AD) have been demonstrated in AD patient CSF. In order to measure accurately and reproducibly these markers in CSF and blood, there is a need for highly sensitive technologies. Recently, ultrasensitive single molecular array (Simoa) immunoassays have been developed for the detection of candidate AD markers t-Tau, pTau231, and Aβ42, and the neuronal damage marker neurofilament light chain (NF-L). In this study, to more fully assess assay analytical performance and characterize the protein markers in human CSF (n=34) and AD plasma (n=42), single molecular array 2-site immunoassays utilizing microwell and magnetic bead digital technology (Quanterix Simoa) were applied for the quantitative measure of proteins t-Tau, pTau231, Aβ42, and NF-L. EDTA-plasma sample groups consisted of 26 moderate-advanced AD (MMSE 4-14), 16 mild cognitively impaired AD (MMSE 18-26), and 16 healthy controls. Concentrations (pg/mL) were determined with dilutions of 100x for CSF and 4x for EDTA-plasma. Plasma t-Tau and NF-L were significantly elevated in moderate-advanced AD relative to mild AD and healthy control samples. NF-L levels were also

significantly elevated in mild AD relative to healthy controls whereas t-Tau levels were not. Plasma Aβ42 was elevated in moderate-advanced AD relative to mild AD and healthy controls. Plasma t-Tau is significantly correlated with NF-L and more weakly with Aβ42, while NF-L weakly correlates with Aβ42. Plasma pTau231 is detectable only in a small percentage of samples. All three plasma markers correlate to variable degrees with age and require a larger sample set and analysis to confirm this relationship.
In CSF, the concentration of all four markers is much higher than in plasma. CSF t-Tau is correlated significantly with CSF NF-L but not with CSF Aβ42, nor does NF-L correlate with Aβ42. CSF pTau231 is significantly correlated with CSF t-Tau. CSF t-Tau, pTau231, and NF-L correlate with age whereas CSF Aβ42 and age weakly correlate.
In summary, all four neuronal markers in CSF and three neuronal markers in EDTA-plasma were reproducibly detected with Quanterix Simoa assays with variable dynamic ranges whereas there is limited detection of pTau231 in plasma. Moderate/advanced AD plasma samples were significantly elevated in levels of t-Tau, Aβ42, and NF-L, and correlations between t-Tau and NF-L levels in CSF and plasma are observed.

Disclosures: **A. Chenna:** A. Employment/Salary (full or part-time):; Monogram Biosciences, LabCorp, Inc. **C.J. Petropoulos:** A. Employment/Salary (full or part-time):; Monogram Biosciences, LabCorp Inc. **J.W. Winslow:** A. Employment/Salary (full or part-time):; Monogram Biosciences, LabCorp, Inc.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.15/O4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AG023084

NS034467

NS100459

AG052350

P50AG005142

Title: Neurovascular dysfunction precedes cognitive impairment independent of Aβ and tau CSF biomarkers

Authors: ***B. V. ZLOKOVIC**[1], M. D. SWEENEY[1], D. A. NATION[1], A. MONTAGNE[1], A. P. SAGARE[1], M. G. HARRINGTON[3], D. BUENNAGEL[3], H. C. CHUI[2], C. Y. LIU[2], J. PA[2], M.

LAW[2], T. L. S. BENZINGER[4], A. M. FAGAN[4], J. C. MORRIS[4]
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Abstract: Increasing evidence supports that cerebrovascular dysfunction contributes to several neurodegenerative disorders, including Alzheimer's disease (AD). Animal studies have shown that pericytes, mural cells of brain capillaries, play a critical role in maintaining blood-brain barrier (BBB) integrity and cerebral blood flow, and pericyte degeneration leads to BBB breakdown and contributes to the neurodegenerative process. Recent neuroimaging studies in the living human brain have indicated BBB breakdown early in individuals with mild cognitive impairment (MCI) and AD, confirming neuropathological findings demonstrating BBB dysfunction and pericyte degeneration in AD. Here, we investigated a novel cerebrospinal fluid (CSF) biomarker of mural cell injury, soluble platelet-derived growth factor receptor-β (sPDGFRβ), in 137 older adults representing individuals with clinical dementia rating (CDR) scale of 0, 0.5 and 1. We evaluated whether mural cell and pericyte injury predates CSF amyloid-β (Aβ) and phosphorylated tau (pTau) changes, and can independently predict BBB breakdown and cognitive impairment. Findings indicate progressive increase in CSF sPDGFRβ levels with clinical progression of subjective cognitive impairment (CDR 0 < 0.5 < 1) as well as objective cognitive impairment which is measured as the number of cognitive domains (i.e., attention, executive function, processing speed, language) impaired on analysis of timed neuropsychological tests. CSF sPDGFRβ levels increased with subjective and objective cognitive impairment. Importantly, these observations were irrespective of CSF Aβ and pTau status, suggesting that mural cell dysfunction and BBB permeability that associated with clinical symptoms of cognitive impairment may operate through an Aβ-independent and tau-independent mechanism. These results suggest that CSF sPDGFRβ is a promising and sensitive biomarker reflective of mural cell dysfunction. Altogether, these findings support that pericyte injury and neurovascular dysfunction may be involved in the earliest clinical manifestations of cognitive impairments, including worsening memory, executive function and language abilities.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.16/O5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Characterization of biofluid sTrem2 using a novel sTrem2 assay

Authors: *J. W. RYDER[1], N. PROCTOR[2], R. SPENCER[2], C. HERSLEY[2], F. TINGLEY[2], S. RAINES[2], S. KUHSTOSS[2], A. MCCONNELL[2], M. HAYASHI[2], Y. WANG[2], M. O'NEILL[2], H. WANG[2]
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Abstract: Genetic variants of triggering receptor expressed on myeloid cells 2 (TREM2) have been linked to Alzheimer's disease (AD) and other neurodegenerative diseases. TREM2 is expressed as a transmembrane protein on the surface of myeloid cells, including microglia from the brain. sTREM2 (soluble TREM2) lacking the transmembrane domain can be detected in the extracellular space as a product of either enzymatic cleavage or alternative splicing. Recently, sTREM2 in cerebral spinal fluid (CSF) has been shown to be elevated in early AD, suggesting sTREM2 is a candidate biofluid biomarker for AD. To date, well validated and sensitive assays to measure sTREM2 are limited. Here we aimed to better understand the biology of sTREM2 release from monocytic cells as well as characterize plasma and CSF biofluid sTREM2 levels. As part of this effort, we also investigated the sTREM2 levels in AD animal models to include both brain and biofliuds. In order analyze sTREM2 levels in conditioned media, biofluids and brain, we developed and validated a robust novel sTREM2 assay using the MSD platform. Indeed, this assay specifically detects sTREM2 with a LLOD of ~6 pg/mL sensitivity. Using this assay, endogenous sTREM2 was analyzed in cell media, mouse plasma, mouse CSF, mouse brain lysate, human plasma, and human CSF. In addition, immunoprecipitation and Western Blotting (IP/WB) were also employed to characterize sTREM2 in biofluid and brain. We demonstrate that sTREM2 is constitutively released from monocytic cell lines in vitro and is readily detectable in rodent brain and in both rodent and human plasma and CSF. IP/WB reveals sTrem2 runs as smeared bands around 25-50 kDa on SDS PAGE. Levels of sTREM2 measured by MSD and IP/WB align well. In mouse, sTREMrem2 levels increase in biofluids with age, but there is no correlation observed between CSF and plasma. sTREM2 levels in biofluids and brain tissues from AD animal models were examined and their relationship with pathology was analyzed.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

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Program#/Poster#: 128.17/O6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH - AG043503

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Penn Institute on Aging

Dana Foundation

Title: TDP-43 co-pathology in alzheimer's disease is associated with cortical thinning

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Abstract: Alzheimer's Disease (AD) is neuropathologically characterized by amyloid-beta plaques and neurofibrillary tau tangles (NFTs). Recent evidence suggests that as many as 19-57% of AD patients additionally have TAR-DNA binding protein of 43kDa (TDP-43) co-pathological inclusions. However, the neuroanatomic consequences of TDP-43 co-pathology are unknown. We evaluated MRI measurements of cortical thickness in 56 patients who were pathologically classified with AD by a board-certified neuropathologist using published criteria. MRIs were obtained approximately 4.4 (±2.7) years prior to autopsy. Additionally, we evaluated TDP-43 pathological inclusions in neuroanatomic loci associated with previously proposed stages of TDP-43 co-pathology progression: (1) amygdala, (2) entorhinal cortex and subiculum, (3) dentate gyrus,(4) insula and inferior temporal lobe,(5) substantia nigra and (6) basal ganglia and middle frontal lobe. Each of the 56 patients were assigned to a TDP-43 stage. We then performed a whole-brain linear regression relating voxelwise measurements of cortical thickness to TDP-43 stage using permutation-based testing, controlling for age at MRI and duration between MRI and autopsy (all $p<0.05$, voxel extent > 50). Relative to AD with TDP-43 co-pathology, no significant cortical thinning was observed in AD patients while the reverse comparison highlighted widespread structural reductions. The regression analysis showed that increasing stages of co-pathology were associated with cortical thinning encompassing amygdala, entorhinal cortex, hippocampus, cingulate gyrus, middle and superior frontal gyrus, inferior and middle temporal gyrus. These results suggest that co-occurring TDP-43 pathology may contribute to the neuroanatomical features of AD. In particular, the observed pattern of cortical thinning suggests more severe limbic and neocortical structural degeneration related to pathological spread. Together, we conclude that widespread cortical thinning associated with TDP-43 co-pathology might represent an important mediator of clinical heterogeneity and disease progression that should be considered in the context of AD-related clinical trials.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.18/O7

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A CSF proteomic screen links retromer to Alzheimer's pathogenic pathways and suggests endosomal-trafficking biomarkers

Authors: *J. NEUFELD, E. CHEN, S. SMALL
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Abstract: While biomarkers exist for the histological hallmarks of Alzheimer's disease (AD)—amyloid plaques and neurofibrillary tangles—currently lacking are biomarkers for endosomal traffic jams, a cytopathological hallmark now thought to play a pathogenic role in AD. With this goal in mind, we used the CAMK2A-CRE system to genetically engineer knockouts of VPS35, retromer's core protein, in the forebrain neurons of mice. We isolated high quality CSF from KOs and controls, performed a proteomic screen using mass spectrometry, and subsequently validated hits via immunoblot in additional cohorts. **Methods:** CSF was collected from 6-month-old male mice, assessed for blood contamination via hemoglobin ELISA, and pooled into biological replicates of 30uL each (5 KO vs 4 control). Pooled CSF samples were analyzed by shotgun mass spectrometry approach using the Thermo Orbitrap Fusion Tribrid mass spectrometer. **Results:** In total, 1505 proteins were identified and over 30 proteins were significantly altered in the CSF of the KO mice. Two classes of elevated proteins were of particular interest: the first is a group of apolipoproteins (ApoE, ApoJ/clusterin, and ApoD), which have established roles in cholesterol transport and have previously been implicated in AD pathology. The second group comprises substrates (CHL1, APLP1, and APLP2) of BACE1, the enzyme which initiates amyloidogenic processing of APP in the endosome. To confirm and validate these findings, we then turned to immunoblot analysis using CSF isolated from a separate cohort of mice. Consistent with the mass spectrometry data, we observed significant increases in CSF levels of ApoE, clusterin, and CHL1 and a trend toward increase in APLP1. **Discussion:** Our results suggest that endosomal trafficking and cholesterol metabolism, two genetic factors linked to AD, might interact in the brain. We are currently testing our hits in human CSF samples to determine whether they can be developed as biomarkers of endosomal-trafficking.

Disclosures: J. Neufeld: None. **E. Chen:** None. **S. Small:** F. Consulting Fees (e.g., advisory boards); Scientific advisory board member for Denali Therapeutics and Janssen Pharmaceuticals.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.19/O8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: A novel multiplex technology for the simultaneous quantification of inflammation markers, and β-amyloid and tau proteins in biological samples

Authors: S. MATYSIAK[1], D. MINCZAKIEWICZ[1], S. PERESON[1], L. DEMEYER[2], H. VANDERSTICHELE[3], B. OLSSON[4], K. BLENNOW[4], *J. SHE[1]
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Abstract: Background: (Neuro)Inflammation is nowadays considered (i) a potential driving factor for Alzheimer's disease (AD) progression or (ii) to be responsible for side-effects in clinical trials. In order to obtain a comprehensive understanding of possible interactions between the immune system and the nervous system, a syndromic approach is needed by quantitating classical neurodegenerative disease and inflammation markers in well-characterized clinical samples. The outcome of such observational studies could reveal new disease pathways and aid in new therapeutic approaches. However, this approach requires the availability of an open platform with flexibility in assay design.
Goal: This feasibility project aimed to transfer protein assays (β-amyloid (Aβ), tau, cytokines) to a novel multiplex platform for use with several biological fluids.
Methods: Evalution™ is an open platform that allows both kinetic and end-point biomarker measurements in a multiplex mode. The system employs reaction-limited binding kinetics by integrating digitally encoded microparticles into microfluidic flow chambers. This controlled microfluidic environment leads to short assay times, high assay accuracy and precision, while using small sample volumes.
Results: The technology and its test procedure allow a fast screening and selection of monoclonal antibodies for use in single or multiplex assay formats. Selection of each antibody pair is done for each analyte separately, taking into account the required assay format, as well as the intended use for the protein. Details on process optimization and in-process quality control will be presented. Assays were designed for different sample types (e.g. CSF, plasma/serum, cell culture supernatant, brain homogenates). Selectivity and specificity is documented by performing studies in single or multiplex mode for several protein panels. In one panel, CSF assays for Aβ isoforms and tau were combined. The ratio of Aβ1¬42/Aβ1¬40 can be quantified using the same sample dilution factor within approximately one hour total assay time. Another panel for plasma/serum combined assays for GM-CSF, IFN-gamma, IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-alpha. Performances of the different assay designs will be presented.

Conclusions: The new Evalution™ platform provides flexibility and simplicity for biomarker integration and analysis in different biological fluids. By using a syndromic approach interactions between biomarkers for neurodegeneration and inflammation can be studied with limited consumption of precious sample. The field of neurodegeneration can take advantage of the possibilities of this new technology.

Disclosures: S. Matysiak: F. Consulting Fees (e.g., advisory boards); MyCartis. **D. Minczakiewicz:** A. Employment/Salary (full or part-time):; MyCartis. **S. Pereson:** A. Employment/Salary (full or part-time):; MyCartis. **L. Demeyer:** A. Employment/Salary (full or part-time):; ADx neurosciences. **H. Vanderstichele:** F. Consulting Fees (e.g., advisory boards); MyCartis. **B. Olsson:** None. **K. Blennow:** None. **J. She:** A. Employment/Salary (full or part-time):; MyCartis - Full-time. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MyCartis.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.20/O9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS KAKENHI Grant Number 15K09808

Title: Low methylation rates of SNCA gene intron 1 in dementia with Lewy bodies patients

Authors: *J. IGA, Y. YOSHINO, Y. FUNAHASHI, K. YAMAZAKI, Y. MORI, T. MORI, S.-I. UENO
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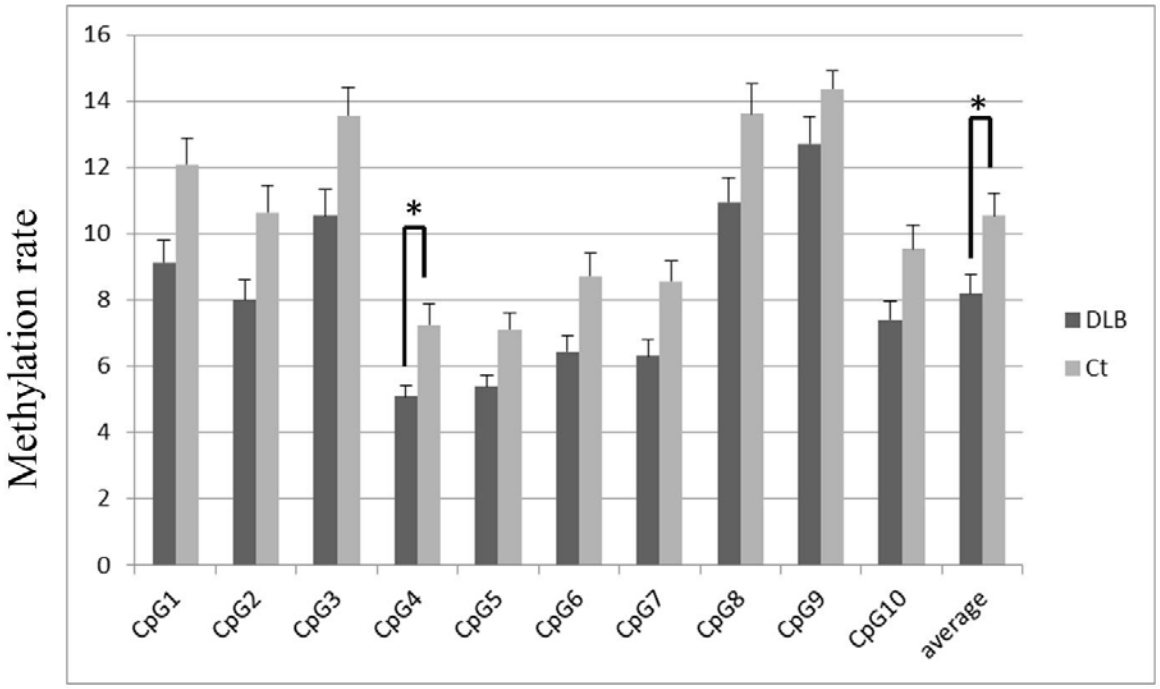
Abstract: It is difficult to diagnose dementia with Lewy bodies (DLB) because of the clinical and neuropathological overlap with both Alzheimer’s disease (AD) and Parkinson's disease (PD). The α-synuclein is a major protein component in Lewy bodies and accumulation of α-synuclein aggregates causes synaptic dysfunction in DLB. Epigenetic changes of α-synuclein gene may be involved in the pathogenesis. Thus, we compared DNA methylation rates of 10 CpG sites located in intron 1 of *SNCA* and *SNCA* mRNA expression in peripheral leukocytes between DLB patients (n = 20; 9 males, 11 females; age = 78.8 +/- 7.7) and healthy controls (n = 20; 8 males, 12 females; age = 77.0 +/- 6.9). The methylation rates of CpG 1 (p = 0.010), 2 (p = 0.009), 3 (p = 0.015), 4 (p = 0.002), 5 (p = 0.007), 6 (p = 0.009), 7 (p = 0.015), and average (p = 0.013) were significantly decreased in DLB patients compared to healthy controls. However, there was no significant difference in *SNCA* mRNA expression between DLB patients and healthy controls (p =0.165). The lower methylation rates of *SNCA* in leukocytes of DLB patients may be useful as a diagnostic biomarker.



Disclosures: **J. Iga:** None. **Y. Yoshino:** None. **Y. Funahashi:** None. **K. Yamazaki:** None. **Y. Mori:** None. **T. Mori:** None. **S. Ueno:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

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Program#/Poster#: 128.21/O10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH K99/R00 AG034214

Title: DNA methylation of tau phosphorylation pathway genes in Alzheimer's disease

Authors: *J. A. ZAHRATKA[1], M. SHAW[1], M. KHRESTIAN[1], J. PILLAI[2], J. B. LEVERENZ[2], L. M. BEKRIS[1]
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Abstract: Alzheimer’s disease (AD) is the most common form of dementia. One of the hallmarks of the disease is neurofibrillary tangles made of hyperphosphorylated tau in the brain. Tau phosphorylation is under the control of many kinases and phosphatases, the regulation of which is not well understood. In this study, we hypothesized that changes in DNA methylation of

kinases and phosphatases targeting tau could be indicative of AD pathology, specifically correlating with AD biomarkers, including Braak stage, plaque score, cerebrospinal fluid (CSF) amyloid and CSF tau levels. To this aim, we measured DNA methylation levels in cerebellum, hippocampus, and whole blood using the Illumina HumanMethylation450K platform, and performed regression analyses. While there were no significant methylation sites in our pilot brain or blood cohorts with respect to disease status, multiple differentially methylated regions (DMRs) were present in our samples associated with biomarkers. Furthermore, several other DMRs were associated with age and sex in both brain and blood. Together, these exploratory data will help illuminate the complicated regulatory networks present in AD, and reveal potential changes in DNA methylation in kinase and phosphatase genes.

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Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.22/P1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Center for Chronic Disorders of Aging

Adolph and Rose Levis Foundation for Alzheimer’s Disease Research

Title: Evaluation of cognition, smell and miRNA biomarkers in Alzheimer’s Disease (AD)

Authors: *V. VALDIVIA[1,2,3], C. J. HAMMOND[1,3,4], K. E. GALLUZZI[1,3,5], S. LEVIN ALLEN[1,3,6], B. J. BALIN[1,2,3]
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Abstract: **Introduction:** While it has been long speculated that traumatic brain injury (TBI) can lead to an increased risk of Alzheimer’s disease (AD), the association of TBI has only been confirmed with an increased risk of dementia, not specifically AD. Interestingly, previous studies have shown that many neuropathologies resulting from a TBI may be regulated by miRNAs . Dysregulated miRNAs have been identified in cerebral spinal fluid and serum from AD patients. Recently, in other pathologies dysregulated miRNAs from saliva have been profiled suggesting that this may also be possible in AD and TBI.
Objective: This pilot study evaluated the potential for using a combination of cognitive and smell testing, and miRNA isolated from saliva as biomarkers in the diagnosis of AD. This could lead to a non-invasive procedure that correlates biomarkers directly to TBI or AD for a diagnosis

of disease.
Methods: Subjects first were evaluated using a St. Louis University Mental Status (SLUMS) exam, followed by collection of saliva and administration of the University of Pennsylvania Smell Identification test (UPSIT). Saliva was treated with protectant (Qiagen) for stabilization of miRNA that was subsequently extracted from AD and control subjects. cDNA from samples was used to run a pre-loaded Human Inflammatory Response & Autoimmunity Qiagen miScript miRNA PCR Array using the StepOnePlus™ Real-Time PCR System (Applied Biosystems™ ThermoFisher Scientific). The Qiagen analytical program was used to analyze data from miRNA arrays to determine expression results from AD/TBI subjects in comparison to controls. This program used the ΔΔCT method of relative quantification.
Results: Individuals with low SLUMS scores also had low smell test scores. miRNA analysis for inflammation between age and gender matched individuals showed a significant difference in the fold change between AD, AD/TBI and controls. Interestingly, both the AD and AD/TBI subjects, as compared to the control, revealed a greater number of down-regulated miRNAs in comparison to up-regulated miRNAs out of 84 examined.
Conclusion: Evaluation of saliva for miRNA was successful. Preliminary data indicate that there is correlation between the SLUMS exam and UPSIT. Changes in miRNA regulation between AD and AD/TBI when compared to control groups were significant. This pilot study evaluating the potential for using a combination of cognitive and smell testing, and miRNA isolated from saliva suggests that there is potential for these to be biomarkers in the diagnosis of AD and AD/TBI.

Disclosures: V. Valdivia: None. **C.J. Hammond:** None. **K.E. Galluzzi:** None. **S. Levin Allen:** None. **B.J. Balin:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.23/P2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Wrenn Clinical Scholars Program

Title: Sex differences in proteomics of early Alzheimer's Disease

Authors: *S. SRIVATSA, J. LUCAS, M. DORAISWAMY
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Abstract: BACKGROUND: Women may have a greater risk for Alzheimer's disease (AD) and there is interest in examining potential sex differences in AD biomarkers. While prior studies have focused on brain imaging or cerebrospinal fluid, there is also a need to validate personalized blood biomarkers. METHODS and RESULTS: We analyzed baseline clinical and

cognitive data from the Alzheimer's Disease Neuroimaging Initiative (ADNI-1) as well as baseline proteomics data in individuals with MCI, AD or normal cognition. A sample of 483 ADNI-1 patients (53 CN, 338 MCI, 92 AD) with baseline proteomics data was analyzed for diagnosis and sex related differences. This 190 analyte multiplex immunoassay panel, referred to as the human discovery map, was developed on the Luminex xMAP platform to contain proteins previously reported in the literature to be altered as a result of cardiovascular disease, metabolic disorders, inflammation, cell signaling and neurodegeneration. Details of the assay technology and validation has been described elsewhere. We conducted statistical analyses to examine if there were sex differences in plasma protein signatures and whether such signatures were related to diagnosis(CN, MCI, AD) and pathological markers. CONCLUSIONS: In initial analyses, a number of protein markers differed by both diagnosis and gender. The top 10 proteins found to differ in AD in order of significance, were Proinsulin (intact), Tenascin C, Epidermal growth factor, Proinsulin (total), Eotaxin 3, CD40L, Platelet derived growth factor BB, Growth regulated alpha protein, Epidermal derived neutrophil activating peptide 78, and C peptide. Discovering sex specific biomarkers may provide novel mechanistic insights into disease modification in subjects at risk.

Disclosures: S. Srivatsa: None. **J. Lucas:** A. Employment/Salary (full or part-time):; Duke University. **M. Doraiswamy:** A. Employment/Salary (full or part-time):; Duke University.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.24/P3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Cytokines as peripheral biomarkers in neurodegenerative disorders: Plasma and CSF analysis of patients with mild cognitive impairment

Authors: *C. W. MCDONNELL, T. BURKE, J. A. PRENDERVILLE, M. BIANCHI
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Abstract: Mild cognitive impairment (MCI) is a syndrome wherein a person experiences greater cognitive decline than is normal for their age. MCI often progresses to more severe conditions such as dementia and Alzheimer’s disease (AD). MCI is estimated to effect 3-19% of adults over 65 and has no reliable treatments options (Gauthier *et al.* 2006). Neuroinflammation is a well-known feature of MCI and proinflammatory cytokines such as IL-1β and IL-6, and TNF-α are linked to progression into AD. There remains a lack of consensus as to which of these markers are up- or downregulated in cerebrospinal fluid (CSF) and blood plasma in MCI individuals. Few studies have investigated these markers in CSF and plasma from the same individuals using multiplex assays. Here, we have analysed the previously mentioned markers and seven additional

proinflammatory markers (IGN-γ, IL-10, IL-12p70, IL-13, IL-2, IL-8, and IL-4) in a multiplex assay, using blood plasma and (CSF) from the same donors diagnosed with MCI and healthy controls.
CSF and blood plasma from donors diagnosed with MCI (n=10) and aged matched controls (n=10) were purchased from a biobank. Expression of cytokines, total tau and amyloid-beta (Aβ) was assessed using MesoScale Discovery systems. Donors also supplied a complete history and completed the mini-mental state examination (MMSE) and Alzheimer's disease assessment scale (ADAS).
The MCI group showed significant deficits in both the MMSE ($p<0.001$) and ADAS ($p<0.001$) compared to healthy controls. The MCI group had a significantly higher concentration of total tau ($p<0.001$) and significantly lower concentration of Aβ ($p<0.05$) in the CSF compared to healthy controls. MCI CSF Aβ levels correlated significantly ($p<0.05$) with MCI CSF total tau. TNF-α concentration was significantly higher in the CSF for MCI compared to healthy controls ($p<0.05$) but there was no difference in TNF-α in the plasma. No significant differences were found with the other markers in the CSF or plasma. A significant correlation ($p<0.05$) was found between MCI CSF IL-1b and MCI CSF total tau but not in healthy controls.
This study is one of the few to use an optimised multiplex assay on plasma and CSF from the same MCI individuals (Brosseron *et al.* 2014). In line with the literature CSF total tau and Aβ were increased and decreased, respectively, confirming the progression of neurodegeneration. TNF-α has been previously reported to be upregulated in CSF of AD patients. The increase of TNF-α in the CSF in our MCI cohort suggests TNF-α plays a major role in the progression to AD. These results demonstrate the importance of using multiplex assays and using CSF and plasma from the same donors during longitudinal studies.

Disclosures: C.W. McDonnell: A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **T. Burke:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **J.A. Prenderville:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd..

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.25/P4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Ventricular volume in Frontotemporal Dementia and genetically at-risk family members: Results from the GENFI study

Authors: *T. P. TAVARES[1], D. G. V. MITCHELL[2], R. BARTHA[2], J. VAN SWIETEN[3], D. GALIMBERTI[4], C. GRAFF[5], M. TARTAGLIA[6], F. TAGLIAVINI[7], J. B. ROWE[8], R.

LAFORCE, Jr[9], G. B. FRISONI[10], A. DE MENDONCA[11], S. SORBI[12], B. BORRONI[13], M. MASELLIS[14], J. ROHRER[15], E. FINGER[2]
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Abstract: Introduction: Frontotemporal Dementia (FTD) is a highly heritable neurodegenerative disorder characterized by drastic changes in behaviour and/or language abilities. As clinical trials of potential disease modifying treatments are currently underway, it is pertinent to identify (1) biomarkers that can help detect at-risk individuals and (2) biomarkers that can be used as surrogate outcome measures to track and assess the effectiveness of future treatments. Current research in Alzheimer's disease has recognized the brain's ventricular volume as a possible biomarker to identify individuals at-risk for developing the disorder and to index the progression of the disease. While cortical volume differences between presymptomatic mutation carriers and non-carriers have been observed 10 years prior to disease onset (Rohrer et al, 2015), no study has assessed ventricular volume expansion in presymptomatic mutation carriers in FTD. The current study addresses this knowledge gap by delineating the progression of ventricular expansion in presymptomatic mutation carriers and in patients who have been diagnosed with FTD. The central hypothesis is that ventricular volume expansion will be greater in presymptomatic mutation carriers and affected patients relative to individuals without the FTD-causing mutations. **Methods and Preliminary Results:** 130 T1-weighted MRI scans of participants who are known carriers of an FTD-causing mutation (*MAPT, Progranulin or C9ORF72*) or a first-degree family member of a known mutation carrier were collected at baseline and approximately 1 year later. Volumetric analysis was conducted using the fully-automated longitudinal processing stream in Freesurfer and for comparison, manual checking and editing of the anatomical segmentations. Preliminary observations reveal that presymptomatic carriers show greater ventricular volume relative to non-carriers. Linear mixed-effects models will be reported examining potential differences between the genetic groups and pre-symptomatic carriers vs. noncarriers, while controlling for family membership, site and time to expected symptom onset. Average rates of ventricular volume change as a function of mutation status and anticipated years of onset will also be reported. **Discussion and Conclusions:** The results of this study will describe the pattern of ventricular volume change in FTD and determine its potential utility as a biomarker for predicting disease onset, tracking disease progression and response to treatment.

Disclosures: T.P. Tavares: None. **D.G.V. Mitchell:** None. **R. Bartha:** None. **J. van Swieten:** None. **D. Galimberti:** None. **C. Graff:** None. **M. Tartaglia:** None. **F. Tagliavini:** None. **J.B. Rowe:** None. **R. Laforce:** None. **G.B. Frisoni:** None. **A. de Mendonca:** None. **S. Sorbi:** None. **B. Borroni:** None. **M. Masellis:** None. **J. Rohrer:** None. **E. Finger:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.26/P5

Topic: I.05. Biomarker and Drug Discovery

Support: NIH MH 108591

Title: Resting-state functional connectivity in large-scale brain networks predicts Alzheimer's Disease symptom severity in novel individuals

Authors: *Q. LIN, M. D. ROSENBERG, K. R. YOO, W.-T. HSU, T. P. O'CONNELL, M. M. CHUN
Yale Univ., New Haven, CT

Abstract: Resting-state functional connectivity (rs-FC) is a promising biomarker for Alzheimer's Disease (AD) because it can reveal features of intrinsic functional brain organization relevant to cognitive abilities and disease status (Finn & Constable, 2016). Practically, resting-state fMRI may be less taxing for participants than task-based fMRI or neuropsychological tests. Previous work, however, has revealed limited success in using rs-FC to predict clinical scores related to AD on an individual subject level. Here we employ a novel approach that uses rs-FC to predict AD symptom severity measured by the Alzheimer's Disease Assessment Scale (11 items; ADAS11) in novel individuals. This approach, connectome-based predictive modeling (CPM, Shen et al., 2017), has been shown to predict fluid intelligence (Finn et al., 2015) and sustained attention (Rosenberg et al., 2016) in novel individuals. Here, we applied CPM to a heterogeneous sample of 59 subjects from the Alzheimer's Disease Neuroimaging Initiative, including normal, mild cognitive impairment and AD subjects. First, we measured participants' rs-FC patterns by computing Pearson correlation coefficients between the timecourses of every pair of nodes in a functional brain atlas (Shen et al., 2013). Using leave-one-subject-out cross validation (LOOCV), we identified connections positively correlated with ADAS11 scores across subjects (positive network) and connections negatively correlated with scores (negative network). Linear models based on overall strength in these networks significantly predicted ADAS11 in novel individuals (positive: Spearman's correlation between predicted and observed ADAS11 scores = 0.49, $p = 9.8 \times 10^{-5}$; negative: Spearman's rho = 0.27, p = 0.04). In a second analyses, we tried other functional connectivity features, accordance and discordance, which disentangle the correlation and anticorrelation components of two brain areas' activity (Meskaldji et al., 2015). Using partial least square regression (PLSR) and a LOOCV procedure, we again built models to successfully predict ADAS11 in novel individuals (accordance: Spearman's rho = 0.34, $p = 8.5 \times 10^{-3}$; discordance: Spearman's rho = 0.27, p =

0.04). Our study provides promising evidence that resting-state functional connectivity can serve as a neural index for AD-related cognitive impairment in an aging population.

Disclosures: Q. Lin: None. **M.D. Rosenberg:** None. **K.R. Yoo:** None. **W. Hsu:** None. **T.P. O'Connell:** None. **M.M. Chun:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.27/P6

Topic: I.05. Biomarker and Drug Discovery

Title: A novel method to collect cerebrospinal fluid in the free-moving mice as a preclinical model for biomarker research

Authors: *T. NAKAJIMA[1], S. TAKEDA[2], A. OYAMA[1], Y. ITO[2], H. RAKUGI[1], R. MORISHITA[2]
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Abstract: With the emergence of disease-modifying therapies for neurodegenerative disorders like Alzheimer’s disease, there is an urgent need for the development of better biomarkers detecting early stage of neurodegeneration and predicting rate of progression. Cerebrospinal fluid (CSF) provides direct representation of pathophysiological changes occurring in the central nervous system, and CSF biomarkers have proven to be useful for the diagnosis and prognosis of neurodegenerative disorders. Preclinical work using mouse models would be useful to explore novel CSF biomarkers; however, detailed characterization of CSF proteins has been challenging due to the difficulty in collecting large amount of CSF from mice. Here, we developed a novel technique that allows consistent recovery of CSF in the awake, free-moving mouse. A small incision was made on the dura mater over the cisterna magna and a collecting tube was placed and fixed on the surface of the dura mater that CSF can be drawn via the small hole. We were able to collect large volume of high-quality CSF from the same animal over time. Contamination of brain tissue or blood, which could potentially affect biomarker measurement, was carefully assessed using sensitive methods. This technique would provide the opportunity to identify novel CSF biomarkers using mouse models.

Disclosures: T. Nakajima: None. **S. Takeda:** None. **A. Oyama:** None. **Y. Ito:** None. **H. Rakugi:** None. **R. Morishita:** None.

Poster

128. Biomarkers for Alzheimer's Disease and Related Dementias

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 128.28/P7

Topic: I.05. Biomarker and Drug Discovery

Title: Multiplex immunoassay detection of Alzheimer’s disease biomarkers in cerebrospinal fluid, plasma, and serum

Authors: *A. J. SAPORITA, C. KORNMEIER, J. HWANG
MilliporeSigma, Saint Louis, MO

Abstract: Progressive neurodegenerative disorders such as Alzheimer’s Disease (AD) affect millions worldwide and are becoming more prevalent as the population ages. Monitoring protein biomarkers in cerebrospinal fluid (CSF) of patients with these disorders has been highly beneficial to understanding disease progression. While several CSF biomarkers can reproducibly distinguish normal and diseased samples, CSF is a difficult biological fluid to obtain in research studies. The need for blood-based biomarkers of AD has driven a continuous search for novel candidates. Here we report the development of a multiplex immunoassay to quantitatively measure seven proteins present in both CSF and blood that are involved in neurological disease: Neurogranin, TREM2, ApoE4, FABP3, Ferritin, Angiogenin, and Prion protein. Notably, reports have linked several of these proteins to ApoE, either by direct interaction (ex: TREM2) or by having expression levels that correlate with *APOE* genotype (ex: Neurogranin, Ferritin). The presence of the *APOE4* allele is prominently associated with an increased risk for AD, in comparison to the *APOE2* and *APOE3* alleles. Although these ApoE isoforms differ at only one or two amino acids, our assay was able to distinguish ApoE4 from ApoE2 and ApoE3 with minimal cross-reactivity. As expected, our results demonstrated that expression of ApoE4 protein was highly enriched in AD samples. Using this novel immunoassay, we also measured the other six biomarkers in CSF, plasma, and serum from AD patients and healthy controls. This study demonstrates the value of using multiplex technology to evaluate multiple biomarkers of neurodegeneration across distinct sample types.

Disclosures: **A.J. Saporita:** A. Employment/Salary (full or part-time):; MilliporeSigma. **C. Kornmeier:** A. Employment/Salary (full or part-time):; MilliporeSigma. **J. Hwang:** A. Employment/Salary (full or part-time):; MilliporeSigma.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.01/P8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH SBIR Grant R43AG051299

Title: NYX-2925, a novel NMDA receptor modulator, reversed cognitive impairment induced by either aging or scopolamine

Authors: *A. L. GROSS[1], J. DUNNING[1], E. COLECHIO[1], A. MOGHADAM[2], X.-L. ZHANG[3], P. K. STANTON[3], M. A. KHAN[1], C. CEARLEY[1], J. R. MOSKAL[4,1]
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Abstract: Aptinyx has developed a novel class of small molecule N-Methyl-D-Aspartate (NMDA) receptor modulators with broad applicability across neurologic and psychiatric disorders. NYX-2925 has been shown to enhance the magnitude of hippocampal long-term potentiation (LTP), facilitated learning in a variety of models, demonstrated antidepressant-like properties in the Porsolt forced swim test, and markedly attenuated neuropathic pain in the Bennett CCI model. In the present study, NYX-2925 was evaluated in two models of cognitive impairment: learning impaired aged rats and scopolamine as a pharmacological model.
The magnitude of cognitively-impaired aged (24 month old F344) rat hippocampal LTP was markedly reduced relative to young adult (2 month old F344) rats. Bath application of NYX-2925 to hippocampal slices *in vitro* from both young adult and aged rats was shown to enhance the magnitude of LTP at Schaffer collateral-CA1 synapses compared to untreated control slices. The optimal enhancement was observed at 100 nM in young adult rats and 500 nM in cognitively-impaired aged rats.
In a second set of studies, NYX-2925 was evaluated for the ability to improve learning in two separate novel object recognition (NOR) tasks: a scopolamine (0.25 mg/kg, IP) induced learning deficit model and a temporal deficit (24 h delay) model. In these assays, adult rats were dosed with NYX-2925 (0.01-1mg/kg, PO) 60 minutes prior to the first testing session (T1) and tested again with one of the objects substituted for a novel object (T2) either 1 h later (scopolamine deficit), or 24 h later (temporal deficit). Both pre-treatment with scopolamine and a 24 h delay between T1 and T2 resulted in an NOR deficit in vehicle animals. NYX-2925 improved performance in the NOR temporal deficit model at all doses. NYX-2925 improved NOR in scopolamine treated rats only at the highest dose (1 mg/kg). Another set of rats were tested in the Morris water maze (MWM) spatial learning model, where treatment with NYX-2925 was able to

reverse scopolamine-induced deficits. These data suggest that NYX-2925 has therapeutic potential for treating cognitive deficit-related disorders.

Disclosures: **A.L. Gross:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc. **J. Dunning:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc. **E. Colechio:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc.. **A. Moghadam:** None. **X. Zhang:** F. Consulting Fees (e.g., advisory boards); Aptinyx, Inc. **P.K. Stanton:** F. Consulting Fees (e.g., advisory boards); Aptinyx, Inc. **M.A. Khan:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc. **C. Cearley:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Aptinyx, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aptinyx, Inc..

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.02/P9

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Longitudinal cognitive testing in mouse models of Aβ and Tau toxicity using an automated CognitionWall task

Authors: *M. LOOS[1], *M. LOOS[1], C. M. HELDRING[2], B. KOOPMANS[1], E. REMMELINK[1], M. VERHAGE[4], R. E. VAN KESTEREN[3], A. B. SMIT[5]
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Abstract: Alzheimer’s disease (AD) is characterized by progressive decline in cognitive function mediated by toxic effects of amyloid-beta peptides (Abeta, Aβ), hyperphosphorylated Tau species, or both. For preclinical testing of interventions against the effect of Aβ or Tau it is key to develop robust longitudinal tests in mice that assess cognitive functions relevant to AD.

We previously described an automated one-night CognitionWall discrimination learning task that can be used longitudinally. In this automated home-cage (PhenoTyper)-based task, mice obtain a food reward every fifth time they pass through one of three entrances in a wall placed in front of a reward dispenser (CognitionWall). We previously reported robust learning deficits in transgenic APP/PS1 mice overproducing Aβ, which were rescued by systemic administration of a BACE1 inhibitor (LY2886721). The task likely engages the hippocampus, since it requires short-term and/or working memory as well as pattern separation, which are cognitive functions relevant to AD. Here we used a previously reported hippocampus-specific intervention, to confirm the involvement of the hippocampus in this task. Intra-hippocampal infusion of Chondroitinase ABC in 16 week old transgenic APP/PS1 mice, previously reported to restore cognitive function in this model, restored task performance to wild type levels, confirming a role for the hippocampus in this task. Longitudinal testing of transgenic mice harboring brain-wide overexpression of mutated Tau (P301S) in the PhenoTyper recapitulated previously reported progressive motor function impairments. Performance in the CognitionWall task was tested at longitudinally within the same cohort. Taken together, this study confirms that the CognitionWall discrimination-learning task engages hippocampal function, and allows longitudinal testing to study the effects of Aβ and Tau species on cognitive functions in mice.

Disclosures: **M. Loos:** A. Employment/Salary (full or part-time):; Sylics. **M. Loos:** A. Employment/Salary (full or part-time):; Sylics. **C.M. Heldring:** None. **B. Koopmans:** A. Employment/Salary (full or part-time):; Sylics. **E. Remmelink:** A. Employment/Salary (full or part-time):; Sylics. **M. Verhage:** F. Consulting Fees (e.g., advisory boards); Sylics. **R.E. Van Kesteren:** None. **A.B. Smit:** F. Consulting Fees (e.g., advisory boards); Sylics.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

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Program#/Poster#: 129.03/P10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Cure Alzheimer's Fund - awarded to J.K.

Title: Deciphering the role of the lymphatic-glymphatic connection in aging and in Alzheimer's disease

Authors: *S. DÁ MESQUITA[1], A. LOUVEAU[1], I. SMIRNOV[1], R. C. CORNELISON[2], K. VIAR[1], J. M. MUNSON[2], J. KIPNIS[1]
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Abstract: The brain parenchyma is devoid of lymphatic vasculature. Hence, the excretion of brain metabolic byproducts and waste, such as amyloid beta, is in part achieved through the

dispersion of interstitial fluid along perivascular spaces into the cerebrospinal fluid (CSF). However, the presence of functional lymphatic vessels embedded in the brain meninges challenged the conventional perception of fluid dynamics within the central nervous system (CNS). These lymphatic vessels actively drain both molecules and cells from the CSF into the cervical lymph nodes, serving as a previously unappreciated route of CNS waste clearance. Herein, we show that impaired drainage of CSF, induced by interference with meningeal lymphatic structure and function, impacts on brain fluid homeostasis, which could be relevant in the context of neurodegenerative disorders like Alzheimer's disease.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.04/Q1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: AAP 2014 Grant from the “Association France Alzheimer et Maladies Apparentées”

Title: Fine pattern discrimination deficits have different origins in mouse models of normal aging and alzheimer's disease

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Abstract: A good memory for details is important to differentiate memories of similar experiences happening in our everyday life. One explanation for age-related deficits in memories for specific events is that older adults tend to rely on general features of an experience rather than specific details. This is consistent with their reduced ability to perform fine pattern discrimination in memory tasks based on novelty detection between highly similar objects or object locations. Interestingly, marked deficit in such tasks have also been reported in Alzheimer patients at a very early stage when the pathology progresses from the medial temporal lobe to the hippocampus. Studies in animals and in humans suggest that fine pattern discrimination ability depends on the integrity of the dentate gyrus (DG)-CA3 region and cortical structure of the temporal lobe. Animal studies further suggest a role for adult-born DG neurons. In a memory task based on behavioral detection of subtle changes in object displacements, we showed a progressive drop in performance from mild to severe between the age of 7 to 21 months in C57BL/6J mice and a very rapid drop of performance between 3 and 4 months in the APP SWE model of Alzheimer’s disease. The large difference in the ages of onset for fine pattern discrimination deficits between these models suggest that impaired performance in APP SWE

mice was mainly related to the early progression of its amyloid pathology as opposed to that of aged mice which appeared gradually as a function of age. Accordingly, when mice were treated for 6 weeks with an antibody directed against the amyloid peptide, the deficit in fine pattern discrimination performance of APP SWE mice was completely rescued, whereas the deep deficit of aged C57BL/6J mice remained unaffected by the treatment. Brains were processed for further analyses. Preliminary results suggest that the improvement of APP SWE performance was not mediated through a beneficial effect of passive vaccination on quantitative aspects of adult neurogenesis. Our ongoing studies focus on functional activation of neuronal populations thought to participate in pattern discrimination.

Disclosures: **C. Héraud:** None. **K. Herbeaux:** None. **C. Mursch:** None. **C. Mathis:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.05/Q2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: LEOC Co., Ltd.

Title: Bone marrow-derived mesenchymal stem cells improve memory in mouse models of Alzheimer’s disease by intracerebroventricular administration

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Abstract: BACKGROUND: While cognitive impairment associated with Alzheimer’s disease (AD) is a worldwide problem, effective treatments have not been fully developed. Here we aimed to investigate whether bone marrow derived mesenchymal stem cells (BM-MSC) can improve cognitive impairment in mouse models of AD via intracerebroventricular (icv) injection. METHODS: We used female B6C3-Tg mice (APPswe, PSEN1dE9, 85Dbo/J: APP/PS1) which develop amyloid pathology in the brain and exhibit cognitive decline at age 13 months old. BM-MSC were isolated from SD rats and 1.0×10^5 of BM-MSC was administered in APP/PS1 mice at age 13 months old, 2 times with 2-week intervals via icv injection. At 2 weeks after last injection, Morris Water Maze (MWM) test was performed to evaluate cognitive function and mice were sacrificed for morphological study. We also evaluated the distribution of BM-MSC in the brain by icv administration of PKH-labeled BM-MSC. RESULTS: In MWM test, cognitive impairment observed in APP/PS1 mice was completely improved by BM-MSC injection. In the subiculum region of the hippocampus, increased positive area of Aβ plaques was observed in APP/PS1 mice with vehicle injection (APP/PS1+V) compared to wild type mice (WT), and this

increase was not altered in APP/PS1 mice with BM-MSC injection (APP/PS1+BM-MSC). The number of NeuN-positive neurons in APP/PS1+V was significantly decreased than that in WT, and this decrease was not recovered in APP/PS1+BM-MSC. On the other hand, TNF-α expression in GFAP-positive astrocytes was significantly increased in APP/PS1+V, and this increase was suppressed in APP/PS1+BM-MSC. In electron microscopy, the decrease of synaptic density was found in APP/PS1+V compared to WT, and this decrease was reversed in APP/PS1+BM-MSC. After icv injection of PKH-labeled BM-MSCs, labeled cells were found to be attached to the choroidal plexus in lateral ventricle. CONCLUSIONS: The results suggest that icv injected BM-MSC contributes to repair the damaged astrocytes in AD mice and increase the synaptogenesis, where humoral factors secreted from BM-MSC might have neuroprotective roles by affecting astrocytes and neurons.

Disclosures: M. Nakano: None. **K. Nagaishi:** None. **Y. Mizue:** None. **T. Chikenji:** None. **M. Otani:** None. **M. Fujimiya:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.06/Q3

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Markers of inflammation and cognitive impairment in a sample of the oldest old (80+ years) in Panama

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Abstract: The Latin American and Caribbean region is experiencing significant growth in the aging population. In Panama the geriatric population is gradually increasing as in the rest of the world. Inflammatory mechanisms in the brain may play an important role in cognitive decline in late-life. We are conducting a biomarker-based study to examine risk factors of cognitive impairment in Panamanians. Here we show the results of a cross-sectional analysis of 144 aged individuals 80 years and older (M = 85.8, SD = 4.5) enrolled in the Panama Aging Research Initiative (PARI) study. The following measures were obtained: global cognition was measured with the Mini-Mental State Examination (MMSE), and depression with the Geriatric Depression Scale 30-item version. Age, sex, education, ApoE ε4 allele expression, diabetes, heart disease, history of stroke, history or present use of tobacco and body mass index were assessed. The blood-based biomarkers were measured using non-fasting serum samples and analyzed in

duplicate via a multi-plex biomarker assay platform using ECL on the SECTOR Imager 2400A from Meso Scale Discovery. The biomarkers included were C-reactive protein (CRP), serum interleukin-10 (IL-10), serum interleukin-6 (IL-6), serum amyloid A protein (SAA) and tumor necrosis factor-α (TNF-α). Logistic regression analysis showed that age, education, IL-10 and TNF-α were significant and independent predictors of cognitive impairment. Our findings suggest an association between specific inflammatory markers and cognitive impairment in the oldest old in Panama (80+ years).

Disclosures: **A.E. Villarreal:** None. **S.E. O'Bryant:** None. **M. Edwards:** None. **S. Grajales:** None. **D.C. Oviedo:** None. **M.B. Carreira:** None. **A.R. Perez Lao:** None. **G.B. Britton:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.07/Q4

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Brain aryl hydrocarbon receptor mediates the glutamate transporter reduction and cognitive impairment in chronic kidney disease mouse model

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Abstract: Chronic kidney disease (CKD) is a progressive loss of renal function that gives rise to accumulation of uremic toxins such as blood urea nitrogen and indoxyl-3-sulfate (I3S) in the blood that causes multiple organ pathology. Recent studies indicated that CKD patients suffer from cognitive impairment even for those receive hemodialysis. Notably, I3S toxicity is attributed to its protein-bound property that cannot be removed by hemodialysis, and can penetrate blood brain barrier. The tryptophan-derived I3S is a potent physiological agonist of aryl hydrocarbon receptor (AhR), a ligand-activate transcription factor that can be activated by polyaromatic environmental hormones and endogenous tryptophane metabolites. In this study, we investigated the molecular mechanism of AhR-mediated EAAT2 alteration and the subsequent impact on cognitive function in CKD. Our study established a 5/6 nephrectomy CKD mouse model that has elevated I3S concentration in both plasma. Western blotting of the four brain regions related to the cognitive behaviors indicated that AhR protein is significantly reduced only in the anterior cortex. Molecular studies further revealed that CKD decreased glutamate transporter EAAT2 and increased reactivated astrocytes in the cerebral cortex, with the effect in the anterior cortex attenuated in the nAhRCKO mice. Besides, CKD mice showed

the anxiety-like behavior with normal locomotor activity at 2 months after 5/6 nephrectomy surgery, and progressively developed working memory impairment in novel object recognition test accompanied with the loss of EAAT2 near the CA1 dendrites- Schaffer collateral fibers contact at 4 months after the surgery. In vitro study in primary mouse astrocytes showed that I3S can activate AhR and chronic I3S treatment significantly decreased EAAT2 expression and glutamate uptake activity. In conclusion, our data indicated that the mouse CKD model and the chronic I3S treatment-mimicking in vitro CKD brain model both led to the reduction of EAAT2 to impair the glutamate homeostasis in an AhR-dependent manner, which may contribute to the neuropsychiatric alterations and cognitive impairment in CKD.

Disclosures: **Y. Huang:** None. **C. Lin:** None. **C. Lu:** None. **H. Lin:** None. **P. Hsu:** None. **D. Tarng:** None. **Y. Lee:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.08/Q5

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fundación Benéfica Deveaux Scholarship

Universidad Católica Santa María La Antigua Grant

Title: Association between depressive symptoms and neuropsychological performance in elderly Hispanic adults with normal cognition and mild cognitive impairment

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Abstract: Cognitive impairment and depression in older adults can affect every day life activities, and increase disability and the risk of mortality. The aim of this study was to examine the association between depressive symptoms and neuropsychological performance in elderly adults with normal cognition and mild cognitive impairment (MCI). Seventy-four participants (controls, n=41; MCI, n=33) age 65 and older from the Panama Aging Research Initiative (PARI) cohort were included in this analysis. We assessed health status and function in everyday life activities. Cognition was assessed with neuropsychological tests, which were divided in six cognitive domains including memory, language, global cognition, attention, executive functions and visuospatial abilities. To measure the presence of depression symptoms we used the 30-item Geriatric Depression Scale (GDS). Participants were also genotyped for APOE isoform. Using

linear regression we examined the relationship between the number of depressive symptoms and cognitive domains, controlling for age, education and APOE genotype across the sample. Depressive symptoms predicted global cognition, executive function and attention. Regression models for individual diagnostic groups revealed that in the cognitively normal group, depression was not associated with neuropsychological function, whereas depression was a significant predictor of executive function and attention in the MCI group. Control and MCI groups did not differ in number of depressive symptoms or in expression of at least one copy of ApoEε4. The results of this study are consistent with previous research that highlights the impairing effect of depressive symptoms on cognitive performance in elderly adults with mild cognitive impairment.

Disclosures: **A.R. Perez Lao:** None. **D.C. Oviedo:** None. **M.B. Carreira:** None. **A.E. Villarreal:** None. **S. Grajales:** None. **R. Solís:** None. **N. Tertusio:** None. **G.B. Britton:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.09/Q6

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: USMA GRANT SRUI-CPEI-ID-2015-2016-004

Scholarship Deveaux Foundation

Title: Association between cognitive function, vascular biomarkers and ApoE4 in a Panamanian sample of healthy controls, mild cognitive impairment and Alzheimer’s disease

Authors: *D. C. OVIEDO[1,2], A. E. VILLAREAL[3], S. A. GRAJALES[3], M. B. CARREIRA[3], A. R. PEREZ[1], R. SOLÍS[1], N. TERTUSIO[1], G. B. BRITTON[3]
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Abstract: Vascular pathology and genetic markers such as Apolipoprotein E allele ε4 are risk factors for mild cognitive impairment (MCI) and Alzheimer’s disease (AD). The main objective of this study was to explore the association between vascular biomarkers such as intima media thickness (IMT) and stenosis and ApoE4 and cognitive function in healthy controls, MCI and AD in Panamanians. To our knowledge this is the first study in Panama and one of the only ones in Latin America to study the association among these variables. A descriptive, cross-sectional, observational study was conducted. Participants were 86 aged adults 65 years and older (controls, n=41; MCI=33; and AD=12), enrolled in a prospective study of the Panama Aging Research Initiative (PARI). Participants were assessed with a neuropsychological battery and a

Doppler ultrasound of carotid arteries (n=70), and were genotyped for ApoE4 (n=84). Neuropsychological tests were combined to form the following cognitive domains: global cognition, language, visuospatial abilities, learning and memory, attention and executive functions. Doppler ultrasound was used to estimate the presence of vascular risk factors using the measures of IMT ≥0.9 mm and stenosis in the left carotid artery. Multivariable analyses (controlling for age, education, sex and ApoE4) were used to compare groups and examine associations between cognitive function, vascular markers and ApoE4. Participants with IMT ≥0.9 mm showed poorer performance in learning and memory (p<0.01) and those with carotid stenosis showed poorer performance in language (p<0.01), visuospatial abilities (p<0.01) and attention (p<0.05). There was an association between ApoE4 and global cognition (p<0.01), visuospatial abilities (p<0.05), memory (p<0.05) and executive functions (p<0.05). In Panamanian elderly, IMT, stenosis and ApoE4 are associated with lower cognitive performance in various cognitive domains. Vascular and genetic markers can be useful tools that aid in early diagnosis of AD.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

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Program#/Poster#: 129.10/Q7

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MELO Brain Project

USMA

SNI

SENACYT

Title: Molecular markers of cognitive deterioration in elderly hispanics

Authors: *M. B. CARREIRA[1], D. OVIEDO[2,3,1], A. E. VILLARREAL[1], S. GRAJALES[1], M. EDWARDS[4], S. O'BRYANT[5], G. B. BRITTON[1]
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Abstract: The elderly, at-risk population for dementia will increase rapidly over the next decades primarily in developing economies. Blood-based molecular markers that can predict changes in cognitive health may represent cost-effective approaches to early diagnoses of dementia and cognitive decline. Data were analyzed for 73 participants enrolled in the Panama Aging Research Initiative (PARI) study. The link between neuropsychological test measures and 21 molecular markers from our Alzheimer's disease (AD) blood profile was explored using linear regression models. Participants were evaluated at two time-points, 15.4 (SD=3.5) months apart. A non-fasting blood draw and neuropsychological testing was performed and participants were classified according to the Global Deterioration Scale (GDS). At the first time-point, 47 participants were classified as GDS=1 (no cognitive impairment) and 26 as GDS=2 (subjective cognitive impairment). Linear regressions were used to determine the molecular markers that predict change in GDS score between time-points. In the first model, without biomarkers, male sex, lower levels of education and limitations in activities of daily living predicted greater deterioration. In the second model, with biomarkers, the same significant predictors as in model 1 and serum amyloid A (SAA) protein predicted greater deterioration. SAA has been implicated in a mouse model of amyloidosis and in AD-related neuronal loss and white matter damage. This work represents the first report of blood-based molecular markers that predict progression to worse cognitive states in a non-U.S. Hispanic cohort and sets the stage for the generation of a cost-effective screen for cognitive decline.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.11/Q8

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Emotion processing deficits and behaviour impairment in neurodegenerative disorders

Authors: *I. D. POPIVANOV[1], S. MEHRABIAN[2], K. STOYANOVA[2], M. RAYCHEVA[2], A. JANYAN[1,3], G. TODOROVA[2], H. THONBERG[4], C. GRAFF[4], B. WINBLAD[4], L. TRAYKOV[2]
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Abstract: Different subtypes of frontotemporal dementia (FTD) and Alzheimer's disease (AD) share overlapping features which causes some difficulties in early stage differential diagnosis. New assessment tools are needed to improve early diagnosis of these conditions.

Here we aim to assess emotion categorisation and behavioural changes and in FTD subtypes and non-amnestic AD patients compared with healthy controls.
Twenty four subjects with behavioural variant FTD (bv-FTD), 11 nonfluent primary progressive aphasia subjects (nf-PPA), 10 semantic dementia (SD) subjects, 13 non-amnestic AD individuals, 6 individuals with corticobasal syndrome (CBS), and 19 age-, gender-, and education-matched healthy controls with normal cognitive functioning were recruited in the study. The subjects were diagnosed according to the latest published criteria.
The behaviour of all patients was evaluated via Frontal Behavioural Inventory (FBI) - a quantative caregiver-based scale consisting of 24 behavioural and personality items designed to probe the core behavioural features of FTD. We assessed the facial expression recognition of six basic emotions (anger, disgust, fear, sadness, surprise, and happiness) and a neutral expression, using 48 photographs of faces from the NimStim Face stimulus set. All faces were in frontal view. The stimuli were shown to the participants one by one. They had first to determine the emotional valence of the face (positive, negative or neutral). If the stimulus was not neutral, the participants had to further define the emotion using one of the six basic emotion categories (anger, disgust, fear, sadness, surprise, and happiness).
Behavioural assessment with FBI showed marked differences between the patient groups ($p = 0.0001$, Kriskal-Wallis test). Patients with bv-FTD were the most impaired, followed by those with SD, non-amnestic AD, and nf-PPA groups.
A very similar trend was present in the performance of the emotional valence task. Bv-FTD patients had the most noticeable deficit, the SD and non-amnestic AD groups were less impaired (ANOVA, $p < 0.005$), while nf-PPA patients exhibited preserved performance on this task. Additionally, neutral stimuli showed the strongest discriminating role in bv-FTD in comparison with other groups. Moreover the performance for neutral stimuli was most affected by behavioural change (Spearman Rank correlation, $r < -0.30$).
In conclusion, we suggest that performance on emotion processing tasks combined with behavioural assessment may provide a useful clinical tool in differential diagnosis of non-amnestic AD and FTD subtypes.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Oberlin College Grant in Aid

Oberlin College Rich Grant

Title: Lowering luteinizing hormone increases spatial memory and decreases neuron loss in an Alzheimer's disease model

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Abstract: Luteinizing hormone increases after menopause or ovariectomy (ovx) in females and high levels of LH have been associated with Alzheimer's disease (AD) in humans. The present study explored whether decreasing LH either prior to or after hippocampal damage would help prevent loss of memory and/or loss of hippocampal neurons. To vary LH levels, adult female Sprague-Dawley rats were ovxd and either given vehicle so they had high LH levels or Antide (1mg/kg, sc), a GnRH antagonist that decreases LH levels. To create a model of early AD, neurotoxins amyloid-beta (4 µg) and ibotenic acid (1µg) were stereotaxically infused bilaterally into the dorsal hippocampus. This resulted in four groups: (1) No AD (infusion of vehicle); (2) AD (infusion of neurotoxins); (3) AD+Preventative Antide (injection of Antide 1d prior to infusion of neurotoxins); (4) AD+Restorative Antide (Antide injections every 4-5d beginning 4-5d after neurotoxin infusion). Beginning one week after stereotaxic surgery females were habituated to the test arena and then tested for spatial memory using the Object Location Test with an inter-trial interval of 10min. Animals were tested 3x with 4 -6d between tests and data were averaged. The No AD females showed clear preference for the moved object, indicating good spatial memory. The AD females did not discriminate between moved and unmoved objects. Antide, when injected either1d prior to neurotoxin infusion (AD+ Preventative Antide group) or after neurotoxin infusion (AD+Restorative Antide group) counteracted the effects of the neurotoxin infusion on spatial memory: That is, females again showed a clear preference for the moved object. Animals were then perfused and brains were sectioned. Neuronal cells were identified with immunohistochemistry to NeuN (AbCam AlexaFluor 488, 1:2000) and the number of neurons in the CA1 region were counted. Antide, administered in either a preventative or restorative pattern reversed much of the neuron cell loss in CA1 after neurotoxin infusion. These results suggest that high levels of luteinizing hormone such as those seen after menopause may contribute to the damage seen during AD, and that an LH antagonist could play a preventative or restorative role in treatment of the neuron loss and cognitive impairment seen in Alzheimer's disease.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

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Program#/Poster#: 129.13/Q10

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: JSPS Grant-in-Aid for Young Scientists (B) 17K17811

Title: Prefrontal cortex volume predicts the rate of improvement of non-pharmacological treatment in dementia: Mihama-Kiho Scan Project 2

Authors: *K. TABEI[1], M. SATOH[1], J.-I. OGAWA[2], T. TOKITA[3], N. NAKAGUCHI[4], K. NAKAO[5], H. KIDA[1], H. TOMIMOTO[1]
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Abstract: Objective: To determine whether regional atrophy or neuropsychological factors can predict the rate of improvement of non-pharmacological treatment in patients with mild to moderate dementia.Methods: Forty-six patients with mild to moderate dementia were followed up six-month. Twenty-five subjects performed physical exercise with music (ExM) developed by the Yamaha Music Foundation, and 21 subjects performed cognitive stimulation (CS) using portable game consoles and drills involving easy calculations, mazes, and mistake-searching in pictures. At baseline, the subjects underwent a neuropsychological battery and a brain MRI. At the end of the six-month, the subjects were dichotomized into improvement group (IG) or no improvement group (no-IG) on the basis of their Mini-Mental State Examination score. We compared baseline cognitive function and imaging data using voxel-based morphometry (VBM).Results: IG and no-IG differed in logical memory I of the Rivermead Behavioral Memory Test at baseline in ExM group, whereas IG and no-IG differed in Raven’s Colored Progressive Matrices and functional independence measure at baseline in CS group. VBM comparison between IG and no-IG demonstrated more gray matter tissue loss in the no-IG in the anterior cingulate gyrus in ExM group, the left middle frontal gyrus in CS group.Conclusion: Voxel-based morphometry analysis demonstrated that patients who will not improve in cognitive function by non-pharmacological treatment had a more extensive cortical atrophy than IG patients in the prefrontal area, in which regional atrophy was different by contents of non-pharmacological treatment.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

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Program#/Poster#: 129.14/Q11

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Contributo Fondo Trieste G92I14000190005

Title: Neural correlates of lexical-semantic knowledge of food

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Abstract: The influential sensory/functional hypothesis (SFH) suggested that recognition of living things (LT) relies on sensory properties and recognition of non-living things (NLT) relies on functional information. Here we investigated whether the sensory/functional distinction can apply to food recognition, that is whether recognition of natural food (NF) relies on shared features with LT, and that of processed food (PF) on shared featured with NLT. Moreover, we tested whether eating disorders associated with neurodegenerative diseases correlated with food semantic deficit.
Fifty-nine participants took part in the study: 9 bvFTD patients, 15 AD patients, 9 PPA patients and 26 healthy controls (HC). The same 72 target stimuli (NF, PF, LT, NLT) were used in a naming and a word-to-picture matching to evaluate lexical-semantic processing. Patients also completed the Appetite and Eating Habit Questionnaire (AEQH). Behavioral and imaging data were analyzed with Voxel-based Morphometry, to correlate participants' gray matter (GM) atrophy with behavioral performance.
Behaviorally, patients performed significantly less accurately than HC. Among patients, bvFTD and PPA named PF significantly better than NF. For food, a significant negative correlation between naming and word-to-picture matching accuracy and AEQH scores on the subscales of eating preferences and habits was observed. The anatomical analysis showed that anterior temporal lobes, right occipital cortex and cerebellum were associated with both LT and NF, whereas the inferior frontal gyrus, superior parietal lobule and left pMTG were associated with NLT and PF, consistently with the previous anatomical localization of tools. In addition, alterations in eating preferences correlates with local GM concentration in the left temporal lobe, left orbitofrontal cortex, right insular cortex and right fusiform gyrus, consistent with the hypothesis that semantic deficits may affect eating disorders.
These results are consistent with the SFH, with sensory properties being relevant for recognizing natural entities (LT, NF) and functional features for artificial entities (NLT, PF). Moreover, our

results support the view that food semantic deficits may be responsible of eating alterations in patients with dementia.

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

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Program#/Poster#: 129.15/Q12

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: The effect of ovariectomy on spatial learning and memory performance in APP and APP-PS1 rat models of Alzheimer's disease

Authors: *D. KLAKOTSKAIA[1], R. A. RICHARDSON[1], P. KANCHANAKASET[1], C. HOWE[1], M. TRATCHEL[1], V. WEISE[1], C. AGCA[2], T. R. SCHACHTMAN[1], Y. AGCA[2]
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Abstract: Transgenic animal models have played a crucial role in our understanding of the underlying mechanisms of Alzheimer’s disease, a progressive neurodegenerative disorder that results in synaptic and neuronal loss in regions of the brain responsible for memory and cognition. In this study, the effect of estrogen deficiency on learning and memory was examined in two strains of transgenic female rats that overexpress human beta amyloid precursor protein (APP). Female rats underwent ovariectomy or sham surgeries at 6 weeks of age followed by behavioral assessment in the Barnes maze at 8 months. There were significant genotype and estrogen differences in performance during all three phases of Barnes maze training. Estrogen deficiency resulted in longer latencies during all three phases of Barnes maze training, but had no effect on error performance. Additionally, it was found that singly transgenic APP rats made significantly more errors than Fischer control rats during acquisition training and at the probe test after a 14-day retention interval, while APP rats with an additional presenilin 1 transgene (APP+PS1) made significantly more errors than Fischer control rats during reversal training. In terms of latency performance, singly transgenic APP rats had significantly longer latencies than Fischer control rats during the probe test and significantly shorter latencies than APP+PS1 rats during reversal training. The overall results suggest an overall spatial memory deficit in the transgenic rats compared to the controls and a detrimental effect of estrogen deficiency on spatial learning and memory performance.

Disclosures: D. Klakotskaia: A. Employment/Salary (full or part-time):; Missouri Department of Health and Senior Services. **R.A. Richardson:** None. **P. Kanchanakaset:** None. **C. Howe:**

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Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.16/R1

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R15AG048447

Title: Intermittent versus continuous assessment of attention in APPswe/PS1dE9 mice using a serial reaction time procedure

Authors: *G. DIMARCO[1], B. N. HARRIS[1], A. V. SAVONENKO[2], P. SOTO[3]
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative disease that results in deficits in cognitive function and reduces quality of life. Procedures that model deficits in cognitive function similar to those seen in AD are required for preclinical screening of possible pharmacotherapeutics. The ongoing study is evaluating whether APPswe/PS1dE9 mice, a transgenic (Tg) mouse model of AD-associated amyloidosis, develop deficits in a test of attention (a 3-choice serial reaction time task) as a first step toward eventual evaluation of potential pharmacotherapeutics for AD-associated cognitive impairment. Male and female Tg and non-transgenic (non-Tg) mice were trained to perform a 3-choice serial reaction time task (3CSRTT). On each trial of the 3CSRTT, a nose-poke response during a 1-s illumination of the nose-poke-hole light or within 5 sec after light illumination produced delivery of a food pellet. Responses prior to illumination of the nose-poke light (premature responses), responses to a non-illuminated hole (incorrect responses), or failures to respond within 5 s after light presentation (omission responses) produced a 10-s timeout followed by a new trial. The effects of intermittent vs. continuous testing regimens as well as the impact of occasional high-difficulty probe sessions on the onset and magnitude of attention deficits in the transgenic mice are also being evaluated. Both Tg and non-Tg mice reached performance criteria (>=80% correct) in approximately equal numbers of sessions. Initial results indicate that Tg mice undergoing continuous testing, compared to non-Tg littermates, do not show decreased performance in percent trials correct as of 45 weeks of age. Following breaks in testing, temporary decreases in percent trials correct and temporary increases in percent trials premature and percent trials omitted occurred in both genotypes. During probe sessions, decreasing the duration of light illumination time in the nose-poke-hole slightly reduced percent trials correct and increased percent trials omitted in both genotypes compared to standard testing. Increasing the duration of time prior to onset of the

nose-poke stimulus light increased premature responses in both genotypes. Although performance deficits in attention may develop at more advanced ages, initial results indicate that up to approximately 11-mo of age APPswe/PS1dE9 mice do not develop deficits in attention as assessed in a serial reaction time procedure.

Disclosures: G. Dimarco: None. **B.N. Harris:** None. **A.V. Savonenko:** None. **P. Soto:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

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Program#/Poster#: 129.17/R2

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R15AG048447-01A1

Title: Assessment of short-term memory in the APPswe/PS1dE9 mouse model of Alzheimer's disease-associated amyloidosis

Authors: T. H. WRIGHT[1], B. N. HARRIS[1], A. V. SAVONENKO[3], *P. L. SOTO[2]
[1]Biol. Sci., [2]Educational Psychology, Texas Tech. Univ., Lubbock, TX; [3]Pathology, Johns Hopkins Univ., Baltimore, MD

Abstract: In 2017, it is estimated that five million Americans are living with Alzheimer's disease (AD). AD is a progressive neurological disease that interferes with cognitive function. Currently available treatments for cognitive impairment due to AD are minimally effective and can produce undesirable side effects. Thus, there is a need for better treatments for AD-associated cognitive impairment. Development of treatments for AD-associated cognitive impairment requires preclinical models of AD-associated cognitive impairment. The aim of this study is to evaluate cognitive impairment in a mouse model of AD-associated amyloidosis as a first step toward eventual screening of potential treatments. APPswe/PS1dE9 double transgenic male and female (TG) mice and non-transgenic (non-TG) littermates were trained on a short-term memory delayed-matching-to-position (DMTP) task, in which, food delivery depends upon the correct choice of a previously presented lever. In one group of mice, the continuous testing group, mice were exposed to daily experimental sessions five days a week from approximately 2 months of ages to 18 months of age. In a second group of mice, the intermittent testing group, mice were exposed to daily experimental sessions five days a week from 2 months of age to 6 months of age, 10-12 months of age, and 16-18 months of age. Both TG and non-TG mice learned to perform the task quickly and with high levels of accuracy. In both genotypes, accuracy declined with the delay between sample lever presentation and choice opportunity and the decrease in accuracy with delay was accurately described by a negative exponential forgetting function. As of approximately 45 weeks of age, differences in measures of initial discriminability

and forgetting rate between TG and non-TG mice in both testing groups were not statistically significant although rates of forgetting were consistently higher in TG mice. Time off from testing in the intermittent testing group decreased measures of initial discriminability and increased rates of forgetting transiently in both genotypes. Although more pronounced deficits may develop at later ages, the current results suggest that frequent testing may alleviate the development of deficits in short-term memory in the APPswe/PS1dE9 double TG mouse model of AD neuropathology.

Disclosures: T.H. Wright: None. **B.N. Harris:** None. **A.V. Savonenko:** None. **P.L. Soto:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.18/R3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DIDARP Grant 5R24DA012136-13

Title: Assessing the cyclooxygenase pathway in Alzheimer's disease using the transgenic rat (TgF344-AD) in the development of spatial memory deficits

Authors: *A. ALLIGER[1], P. A. SERRANO[2], P. ROCKWELL[3], M. FIGUEIREDO PEREIRA[3]
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Abstract: Chronic inflammation has a central role in Alzheimer’s disease (AD) and in accelerating AD pathology. A major player in inflammation is the cyclooxygenase (COX) pathway. Cyclooxygenases (COX -1, constitutive; COX-2, inducible) are key enzymes in the conversion of arachidonic acid into bioactive prostaglandins (PGs). In AD, COX-2 is highly induced and its increase correlates with AD severity. Some of the PGs produced by the cyclooxygenase pathway are neuroprotective, while others are neurotoxic. Little is known about the profile and role of PGs in the progression of AD pathology. The new AD transgenic rat (TgF344-AD) presents the full array of AD pathology, including age-dependent cerebral amyloidosis that precedes tauopathy, gliosis, apoptotic loss of neurons in the cerebral cortex and hippocampus, and cognitive impairment. Thus, this TgF344-AD rat model fills the critical need for a next-generation rodent model for use in basic research to advance our understanding of AD. Our goal is to characterize the temporal profile of PGD2, E2 and J2 in the hippocampus during disease onset and progression and to correlate it with hippocampus-dependent behavioral deficits. With this strategy, we expect to identify PGs that serve as potential biomarkers and/or

therapeutic targets for AD. In order to characterize the progressive nature of the memory deficits in this rat model, we tested female TgF344-AD (N=5) and F344 controls (N=5) on the radial eight-arm maze (RAM) for hippocampus-dependent working memory deficits at 7 and 8 mo. Additionally, at 7 mo all subjects were tested for anxiety on the elevated plus maze (EPM). The EPM results show no significant differences between groups across several measures. For the RAM working memory assessment all 8-arms were baited. An incorrect score resulted from animals revisiting an arm twice. We analyzed retrieval of baits 1-4 and 5-8 separately as the first four arms represent an easy cognitive load (ECL) while the second four arms represent a difficult cognitive load (DCL). At 7 mo the TgF344-AD rats show a significant deficit in both the ECL and DCL performance compared to controls ($p<.05$). Additionally, the TgF344-AD show significant deficits in their 8 mo RAM for both their ECL and DCL compared to their 7 mo RAM assessment ($p<.05$). The F344 controls maintain their performance level across the 7 and 8 mo RAM assessments ($p>.05$). These results indicate that at 7 mo of age the TgF344-AD rats are exhibiting working memory performance deficits, which worsen by 8 mo. Our last assessment will be at 11 mo of age, which will be followed by PG analyses, and other markers of neuroinflammation in the hippocampus.

Disclosures: **A. Alliger:** None. **P.A. Serrano:** None. **P. Rockwell:** None. **M. Figueiredo Pereira:** None.

Poster

129. Cognitive Dysfunction in Alzheimer's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 129.19/R4

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CONCyTEP-TESIS-2016 Grant

VIEP 2016-2017 Support

Title: Metabolic syndrome implications on spatial memory and glial cell immunoreactivity induced by injection of amyloid-β 25-35 peptide

Authors: *O. REYES[1], A. PATRICIO-MARTÍNEZ[1], G. MORALES[1], J. PANTLE[1], S. ZARATE[1], F. LUNA[2], I. D. LIMÓN[1]
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Abstract: Metabolic syndrome (MetS) is a group of risk factors that include abdominal obesity, insulin resistance, dysglycemia, raised blood pressure, elevated triglyceride and low high-density lipoprotein cholesterol levels, which occur at younger ages and its prevalence continues to rise.

MetS increases the risk for development Alzheimer's disease (AD). The cognitive impairment and neuroinflammation are determinant factors in the physiopathology of AD and it has been demonstrated experimentally by injection of neurotoxic peptide Amyloid-β $_{25-35}$ (Aβ $_{25-35}$). The aim of present study was examined the impact of MetS for spatial learning and memory and glial cells reactivity induced by injection of $A\beta_{25-35}$ into CA1 subfield. The MetS group was obtained by consumption of 20% sucrose in drinking water, the control group (C) received tap water and all rats fed standard rat chow. The diets were administrated during all experimental protocol. At 8 weeks of consumption, MetS model was characterized by assess zoometric and metabolic parameters, after that all rats were injected with vehicle (SSI) or $A\beta_{25-35}$ [100µM] into CA1 region of hippocampus (Hp), (coordinates; AP: -4.0, L: ±2.3, P: -2.6) in this way, we formed C+SSI, C+$A\beta_{25-35,}$ MetS+SSI and MetS+$A\beta_{25-35}$ groups (*6 per group*). 15 days post-surgery animals were tested for spatial learning and 5 days after the memory test in the Morris water maze (MWM). The brains were obtained to assess glial fibrillar acid protein (GFAP) and the Ionized calcium binding adaptor molecule 1 (Iba-1) by immunohistochemistry in CA1, CA3 and dentate gyrus subfields of the Hp, frontal and temporal cortex (FCx, TCx). The results show that MetS plus intrahippocampal injection of $A\beta_{25-35}$ 100µM, not impair the spatial learning and memory in the MWM. Meanwhile, MetS experimental model with injection of $A\beta_{25-35}$, caused a significant decrease of GFAP immunoreactivity for FCx. In the same way MetS+SSI and MetS+$A\beta_{25-35}$ groups show a significant decrease for Iba-1 immunoreactivity in the CA1 subfield and TCx. Thus, the results indicate that the peripheral metabolic disturbances that describe MetS, by intake of 20% sucrose solution and the injection of $A\beta_{25-35}$ into the CA1 subfield of Hp of rats, not impair the learning and memory tested in MWM in the same way to trigger reactivity of astrocytes and microglial cells in associated cognitive regions to injection site.

Disclosures: O. Reyes: None. **A. Patricio-martínez:** None. **G. Morales:** None. **J. Pantle:** None. **S. Zarate:** None. **F. Luna:** None. **I.D. Limón:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.01/R5

Topic: C.03. Parkinson's Disease

Support: NIH Grant R21DA038384

Title: Differences in the redox coenzyme, NAD(P)H, in nigrostriatal and mesolimbic dopamine neurons

Authors: *K. R. TUCKER[1,2], E. S. LEVITAN[2]
[1]Penn State Greater Allegheny, McKeesport, PA; [2]Pharmacol. and Chem. Biol., Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: Dopamine (DA) neurons of the substantia nigra pars compacta (SNc) are more sensitive to ongoing redox stress than those of the ventral tegmental area (VTA). The pyridine nucleotides NADH and NADPH (together NAD(P)H) are redox coenzymes involved in metabolism, bioenergetics and neurodegeneration. In a recent study, multiphoton microscopy of brain slices was used to take advantage of NAD(P)H autofluorescence in response to far red light. By comparing the autofluorescent signal of different areas of the brain, we found NAD(P)H levels to be 32-40 % higher in SNc DA neurons than other brain regions under the same conditions. Using this technique, SNc DA neurons were compared to those of the VTA to quantify differences in the NAD(P)H levels, determine its distribution, and monitor responses to mitochondrial perturbation. NAD(P)H autofluorescence is significantly lower in VTA DA neuron cell bodies and terminals in the ventral striatum, than in those of SNc cell bodies and their terminals in the dorsal striatum. At a subcellular level, uncoupling and inhibition of the electron transport chain results in significantly larger changes of NAD(P)H autofluorescence in SNc DA neuron mitochondria/endoplasmic reticulum fraction and the nucleus than those of the VTA. In fact, the nuclear fraction in VTA DA neurons does not change in response to the uncoupling agent, FCCP. Since the nuclear concentration should follow that of the cytoplasm, this suggests differential handling of cytoplasmic NAD(P)H levels between the two regions. These preliminary data suggest a fundamental difference in the redox systems of these two closely related dopamine neurons.

Disclosures: K.R. Tucker: None. **E.S. Levitan:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.02/R6

Topic: C.03. Parkinson’s Disease

Support: Brain Research New Zealand

NZ Neurological Foundation

Title: The effects of uptake-2 blockers on stimulated dopamine release in the nigro-striatal pathway after L-DOPA loading

Authors: *J. LLOYD, A. MCDOUALL, M. R. MICHAEL, G. R. LOKE, B. FORBES, P. S. FREESTONE, *J. LIPSKI
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Abstract: Extracellular dopamine (DA) levels in the nigro-striatal pathway largely depend on DA clearance by dopamine transporter (DAT) which belongs to a group of ‘conventional’ high

affinity monoamine transporters collectively referred to as Uptake-1. Another uptake mechanism (Uptake-2) has been identified more recently, which mainly involves two additional transporters: OCT-3 (Organic Cation Transporter 3) and PMAT (Plasma Membrane Monoamine Transporter). These high-capacity, Na^+/Cl^- independent cation transporters are widely expressed in the CNS including the nigro-striatal region, both in neurons and glia. Although they normally remove DA from the extracellular space, they are bi-directional and thus are also likely to mediate release when intracellular neurotransmitter levels are high and/or during depolarization of cell membrane potential. To test this hypothesis, we used a combination of electrophysiological and electrochemical approaches in brain slices containing the Substantia Nigra pars compacta (SNc) or the striatum. Intracellular levels of DA were enhanced by L-DOPA (10 µM), and the DAT-mediated DA uptake was reduced by nomifensine or cocaine. DA release in the SNc region was evoked by burst of stimuli (5 pulses, 2 ms, 40 Hz; every 90 s), and was indirectly detected by recording D2 receptor-mediated (sulpiride-sensitive) transient inhibition of spontaneous firing of dopaminergic neurons or D2-IPSCs (Beckstead et al. 2004, Neuron 42:939) after blocking GABA and glutamate receptors. DA release in the striatum evoked by single electrical stimuli was recorded with fast-scan cyclic voltammetry (FSCV). Stimulated DA release in the SNc was reduced ($p<0.05$; n=6 slices) in the presence of D22 (1,1′-Diethyl-2,2′-cyanine iodide; 25 µM), a known Uptake-2 blocker. As D22 generates its own electrochemical signal which partly overlaps with DA oxidation potential and reduces the sensitivity of carbon fiber microelectrodes to DA, this blocker could not be used in electrochemical recordings conducted in the striatum. Therefore, we are currently studying the effects of other, less electroactive Uptake-2 blockers (including corticosterone) on DA release in that region. Our data obtained so far indicate that after L-DOPA loading a component of stimulated DA release is mediated by reversal of DA transport through Uptake-2.

Disclosures: **J. Lloyd:** None. **A. McDouall:** None. **M.R. Michael:** None. **G.R. Loke:** None. **B. Forbes:** None. **P.S. Freestone:** None. **J. Lipski:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.03/R7

Topic: C.03. Parkinson’s Disease

Title: The rostral pedunculopontine nucleus contributes to M_4R modulation of L-DOPA-induced dyskinesia

Authors: *N. E. CHAMBERS[1], C. SAITO[2], S. LEFKOWITZ[2], A. TAYLOR[2], S. MEADOWS[2], K. CHEMAKIN[2], E. SHEENA[2], C. BISHOP[2]
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Abstract: L-DOPA remains the standard treatment for Parkinson's disease (PD) despite the fact that it produces debilitating abnormal involuntary movements termed L-DOPA-induced dyskinesia (LID). Although the causes of LID are multi-faceted, recent evidence suggests that elevated cholinergic tone contributes to LID. As such, targeting inhibitory M4 muscarinic acetylcholine receptors (M_4Rs) has been shown to reduce LID expression in various preclinical models. Although striatal M_4Rs have been implicated, cholinergic neurons in the pedunculopontine nucleus (PPN) also express M_4Rs and are thought to modulate Parkinsonian motor deficits. In this regard, the rostral PPN (rPPN) is particularly well-situated to modulate LID and motor behavior because it projects to structures such as the thalamus, subthalamic nucleus, and striatum. Therefore, the present study investigated the effects of systemic and local rPPN infusion of the M_4R-preferring antagonist Tropicamide on LID and on L-DOPA's motor efficacy. Hemi-parkinsonian rats displaying LID were employed in two within-subjects experiments. In the first experiment, Tropicamide (0, 3, 10, or 30 mg/kg, i.p.) was administered systemically five minutes before L-DOPA (4 mg/kg, s.c.). In the second experiment, Tropicamide (0, 20, 200 μM) was infused into the rPPN beginning five minutes before L-DOPA administration(4 mg/kg, s.c.). In both experiments, ten minutes after L-DOPA administration, abnormal involuntary movements were rated for one minute every ten minutes for 180 minutes. Additionally, forepaw adjusting steps were rated to evaluate L-DOPA's motor efficacy. The results of the current study demonstrate that systemic Tropicamide administration prolongs the time course of LID without affecting L-DOPA's motor efficacy, and that local Tropicamide infusion into the rPPN mimics these systemic effects. Therefore, M4-receptor-expressing neurons of the rPPN represent a promising therapeutic target for attenuating LID expression without reducing L-DOPA's motor efficacy.

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Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.04/R8

Topic: C.03. Parkinson's Disease

Title: α-Synuclein preformed fibrils (αSyn-PFFs) differentially shape the intrinsic and synaptic plasticity of midbrain dopaminergic neurons

Authors: *G. MADEO[1,2,3], X. MAO[4], Y. YASUI[1], R. A. M. MARINO[1], N. B. MERCURI[2,3], A. PISANI[2,3], V. L. DAWSON[4,5,6], T. M. DAWSON[4,5,7], A. BONCI[1]
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Vergata, Rome, Italy; [4]Inst. for Cell Engin. and Dept. of Neurol., [5]Dept. of Physiol., [6]Solomon H. Snyder Dept. of Neurosci., [7]Dept. of Pharmacol. & Mol. Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: α-Synuclein preformed fibrils (α-Syn PFFs) are a form of misfolded α-Synuclein (α-Syn) that has been causally implicated in Parkinson disease (PD). Previous studies have shown that the degree of neurodegeneration mediated by α-Syn PFFs is dependent on relativeα-Syn expression level, regional connectivity, and cell type. However, the impact of α-Syn PFFs on the intrinsic excitability and synaptic inputs of neurons, and how this contributes to the degeneration of specific neuronal populations, is largely unknown. In PD this differential vulnerability is particularly notable within midbrain dopamine (mDA) neurons in the substantia nigra (SN), whereas mDA neurons in the neighboring ventral tegmental area (VTA) are significantly less affected.

Using a combination of electrophysiological and molecular approaches, we aimed to define the effect of α-Syn PFFs on the intrinsic excitability and synaptic transmission of midbrain dopamine (mDA) neurons from the substantia nigra (SN) and the ventral tegmental area (VTA). We provide evidence that α-Syn PFFs selectively increase intrinsic excitability and depress glutamatergic synaptic transmission onto mDA-SN neurons. In contrast, α-Syn PFFs do not affect either intrinsic excitability or synaptic properties of mDA-VTA neurons. Furthermore, NMDAR-mediated currents in mDA-SN neurons exposed to aSyn PFFs show significantly faster kinetic properties and a decrease of synaptic GluN2B containing NMDAR responses in mDA-SN neurons. These findings suggest that α-Syn PFFs exposure promote a functional switch in subunit composition from GluN2B to GluN2A-containing NMDARs. Finally, blocking NMDARs during α-Syn PFF exposure prevents α-Syn PFF-mediated changes in mDA-SN intrinsic excitability.

Our results suggest that α-Syn PFFs differentially shape the intrinsic excitability and glutamatergic synaptic transmission of mDA-SN neurons through the modulation of NMDAR subunits composition.

This selective effect of α-Syn PFFs induced changes on mDA-SN neurons, mediated by alterations in NMDAR-subunits composition, may be a target for therapeutic and disease-modifying intervention in PD.

Disclosures: G. Madeo: None. **X. Mao:** None. **Y. Yasui:** None. **R.A.M. Marino:** None. **N.B. Mercuri:** None. **A. Pisani:** None. **V.L. Dawson:** None. **T.M. Dawson:** None. **A. Bonci:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.05/R9

Topic: C.03. Parkinson’s Disease

Title: Investigate the neurotoxic effects of the designer drug Tri-Fluoro-Methyl-Phenyl-Piperazine derivatives

Authors: *M. A. MAJRASHI[1,2], M. ALMAGHRABI[1], S. RAMESH[1], D. DESAI[1], M. GOVINDARAJULU[1], V. SUPPIRAMANIAM[1], J. DERUITER[1], C. CLARK[1], M. DHANASEKARAN[1]
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Abstract: The use of piperazine derivative designer drugs have augmented enormously throughout the world. Designer drugs exhibit significant psychedelic effects and can be extremely toxic. Interestingly, the abusers do not have the basic knowledge of the toxic effects of these substances. Presently, designer drugs are casting a cloud over the renaissance of scientific research into legitimate uses for psychedelic drugs. Piperazine derivatives (TFMPP) are presently being consumed and there are very few reports on its neurotoxic effects and the mechanisms associated with its neurotoxic actions. Thus, in this study, we investigated the neurotoxic effects of Tri-Fluoro-Methyl-Phenyl-Piperazine derivatives. TFMPP derivatives were synthesized in our lab. Dopaminergic cell lines (N27 cells) were used to investigate the neurotoxic effects of TFMPP derivatives. The effect of TFMPP derivatives were studied on the markers of oxidative stress, mitochondrial functions and other relevant neurotoxic mechanisms. TFMPP derivatives (2, 3 and 4) dose-dependently inhibited the growth of N27 cells. Also, TFMPP derivatives induced oxidative stress and mitochondrial dysfunction. If the use of the designer drugs are not properly regulated, there is a potential threat towards increasing the risk for movement and mental disorders in the society.

Disclosures: M.A. Majrashi: None. **M. Almaghrabi:** None. **S. Ramesh:** None. **D. Desai:** None. **M. Govindarajulu:** None. **V. Suppiramaniam:** None. **J. Deruiter:** None. **C. Clark:** None. **M. Dhanasekaran:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.06/R10

Topic: C.03. Parkinson’s Disease

Title: Cell-specific spinophilin function following exposure to drugs of abuse

Authors: *D. S. WATKINS[1], A. J. BAUCUM II[2]
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Abstract: Proper synaptic transmission is critical for maintaining neuronal communication. Changes in this transmission is associated with multiple neurological disease-states such as drug addiction. Competent neuronal signaling is maintained by the targeting of specific kinases and phosphatases to the post-synaptic density. To obtain substrate selectivity, phosphatases, such as protein phosphatase 1 (PP1), associate with targeting proteins. The major targeting protein in the postsynaptic density area of dendritic spines is spinophilin. Our lab has found that spinophilin interactions in the striatum are modulated by dopamine depletion; an animal model of PD. Furthermore, data has been shown that there are sex differences in dopaminergic neurotransmission. However, the effects of hyperdopaminergic signaling following exposure to drugs of abuse are less well characterized. Here, we begin to report changes in spinophilin interactions following treatment with drugs of abuse. Moreover, we have generated transgenic spinophilin animals that Cre-dependently express an epitope-tagged, human form of the protein. These animals will allow us to determine if spinophilin interactions are modulated in specific cell types following exposure to drugs of abuse. The implications for regulating spinophilin interactions in specific cell types following drugs of abuse exposure will be discussed. In addition sex differences will be discussed.

Disclosures: D.S. Watkins: None. **A.J. Baucum II:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.07/S1

Topic: C.03. Parkinson’s Disease

Support: CNPq

CAPES-FCT

FAPESC

Title: Apoptosis signaling activation following 6-hydroxydopamine-induced locus coeruleus lesion promotes olfactory, memory and emotional impairments in rats

Authors: *T. B. SAMPAIO, K. ROVERSI, R. N. TAKAHASHI, R. D. PREDIGER
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Abstract: Neurodegenerative diseases, including Alzheimer’s and Parkinson’s disease, display an early and progressive noradrenergic neuronal loss in the *locus coeruleus* (LC), the main source of cerebral noradrenaline. As consequence, decreased noradrenaline levels in many brain areas may be associated with olfactory, cognitive and emotional symptoms observed in Alzheimer's and Parkinson's diseases carriers. 6-Hydroxydopamine (6-OHDA) is a

catecholaminergic toxin largely used to induce neuronal death of dopaminergic and noradrenergic networks. Therefore, the purpose of this study was to investigate the apoptotic signaling activation and the temporal development of behavioral impairments in male adult Wistar rats following a selective noradrenergic lesion of the LC induced by 6-OHDA. In order to carry out a selective noradrenergic lesion, the dopamine transporter inhibitor nomifensine (10 mg/kg/ml, i.p.) was administrated one hour before the stereotaxic bilateral injections of 6-OHDA (5 µg/side) into the LC. SHAM group received just vehicle (0.2% ascorbic acid in saline). The current low dose of 6-OHDA did not cause any motor alterations. Behavioral tests and LC dissection were performed at 7, 21 or 42 days after the surgery. The apoptosis pathway activation was evaluated through the relation between Bax and Bcl-2 immunocontents by western blot assay. 6-OHDA infusion into the LC increased the Bax/Bcl-2 relation in the LC tissue 7 and 21 days after the surgery. Olfactory discrimination was disrupted by 6-OHDA administration after 7 days. Moreover, 6-OHDA induced short-term memory deficit in the step-down passive avoidance task at 7 and 21 days after injection and in the object recognition test in all periods. Long-term memory was disrupted by LC lesion only at 7 days in both cognitive tasks. Lastly, LC lesion induced depressive-like behavior addressed on the forced swimming test at 21 and 42 days after the infusion. Thus, a selective noradrenergic damage of LC induced by 6-OHDA causes apoptosis signalling activation in rats. Moreover, the temporal development of 6-OHDA-promoted behavioral impairments may be an useful experimental tool for investigation of olfactory, memory and emotional changes observed in Alzheimer's and Parkinson's diseases patients.

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Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.08/S2

Topic: C.03. Parkinson’s Disease

Support: JSPS KAKENHI Grant Number 25461296

Title: Proteasome degradation of tyrosine hydroxylase triggered by its phosphorylation: A question on the intracellular location and the degradation

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Abstract: Tyrosine hydroxylase (TH) is the rate-limiting enzyme in catecholamine biosynthesis, and its stability is an important factor to maintain the level of the catecholamines in cells. The

phosphorylation of TH at its Ser19 (pSer19-TH) is supposedly a critical trigger for degradation of the enzyme by proteasomes and is observed mainly in the nucleus of PC12D rat pheochromocytoma cells. However, it is unclear why pSer19-TH is localized in the nucleus and whether this localization relates to proteasome degradation.Therefore, we examined whether a nuclear localization signal (NLS) exists in TH molecules by using cNLS Mapper program (Kosugi et al. 2009). The cNLS Mapper program predicted that N-terminus of the rat TH molecule has two NLS sequences with scores from 3 to 4, being Pro^{9}-Arg^{38} and Lys^{12}-Ile^{42}, in the N-terminal regulatory domain. Again, two NLS sequences were also predicted in the N-terminus of human TH type 1, which possesses almost the same amino acid sequence as rat TH. Scores from 3 to 5 indicate that a protein with the NLS sequence will localize in both nucleus and cytoplasm. Moreover, the phosphorylation of a cargo protein may up-regulate or down-regulate its nuclear import.We next examined whether the inhibition of the importin α/β-mediated nuclear import pathway could increase the level of TH phosphorylated at its Ser19 in PC12D cells. The inhibition of importin-β by importazole significantly increased the level of pSer19-TH in PC12D cells, although the levels of THs phosphorylated at Ser31 and Ser40, and TH molecule did not increase.These results suggest that TH might be imported to nucleus from cytoplasm to be degraded. Recent studies revealed that proteasomes predominantly exist in the nucleus rather than in the cytoplasm to degrade the nuclear proteins related to cell-cycle progression, gene expression, and DNA repair. Therefore, our studies suggest that the relationship between the phosphorylation and the nuclear localization of the TH molecule should be a matter of focus to understand the mechanism of proteasome degradation of the enzyme.

Disclosures: A. Nakashima: None. **Y. Kodani:** None. **Y. Kaneko:** None. **H. Nagasaki:** None. **A. Ota:** None.

Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

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Program#/Poster#: 130.09/S3

Topic: C.03. Parkinson’s Disease

Support: Academy of Finland

3iRegeneration Tekes

Sigrid Juselius Foundation

Title: Implementation of neural networks to quantify substantia nigra dopamine neurons

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Abstract: Making unbiased estimates of total neuron number of specific brain nuclei has been crucial for developmental neurobiology, experimental neurology, aging studies and drug development. It is well accepted that the parameter that allows one to make comparative statements about numbers of neurons is a total number of neurons. Unbiased stereological counting techniques with optical fractionation have been successfully implemented. However, these techniques are extremely laborious and time-consuming. The development of neural networks and deep learning has opened a new way to teach computers to count neurons. Neural networks are a programming paradigm that enables a computer to learn from the data. The advantages of computerized counting are reduced human errors, a decrease in variability, and the faster analysis enables increasing the analysis capacity. We implemented whole slide digital imaging and neural networks to count substantia nigra dopamine neurons. These dopamine neurons die in Parkinson's disease, and the unbiased neuron number counts are a cornerstone of experimental Parkinson's disease studies. We compared the results of this new method to the studies we have previously published in rats and mice. In these previous studies, tyrosine hydroxylase immunoreactive neurons have been counted using stereology (Runeberg-Roos et al Neurobiology of Disease, 2016, Kumar et al PLoS Genet 2015). We present results from our newly developed technique that provide robust and fast analysis of dopamine neurons in rat and mouse substantia nigra. The method provides an efficient and reliable way to count dopamine neurons and therefore estimates the total number of dopamine neurons in the substantia nigra.

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Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 130.10/S4

Topic: C.03. Parkinson's Disease

Support: Drexel Coulter Translational Grant

DA031900

Title: Biased signaling of dopamine D3 receptor agonists influences compulsive behaviors in neurological disorders

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Abstract: Dopamine D3 Receptors (D3Rs) are implicated in the etiology of compulsive and impulsive disorders. Specifically, Akt and glycogen synthase kinase 3β (GSK3β) signaling pathways activated via D3Rs have been evidenced to play a role in the regulation of these disorders. In our previous study, we designed a novel class of D3R agonists that have biased signaling properties via G-proteins but not the β-arrestin pathway. These compounds also do not induce D3R desensitization, suggesting a lack of β-arrestin recruitment. In this study, we investigated the effects of this novel class of D3R agonist SK608 and D2R/D3R agonist Pramipexole (PRX) on Akt/GSK3β in SH-SY5Y cells stably expressing D3Rs. Our results demonstrate that PRX induced significant phosphorylation of ERK1/2, Akt, and GSK3β ser9 reaching a plateau at about 5-10 min and lasting at least 4h. SK608, however, only induced short-term ERK1/2 phosphorylation (in 20 min) and Akt phosphorylation (in 60 min) but had no effect on GSK3β ser9 phosphorylation. This validates that SK608 exhibits G-protein biased signaling, but PRX may signal through both G-protein- and β-arrestin-mediated pathways. In addition, PRX induced desensitization of the ERK1/2, Akt, and GSK3β phosphorylation signal which was not observed with SK608. These results suggest that PRX- and SK608-induced D3R activation involves different signal pathways and may contribute to their differential effects in vivo. The reinforcing effects of SK609 (a SK608 analog) and PRX in vivo were measured using a cocaine self-administration assay, under the fixed ratio (FR1) schedule of reinforcement. Naïve male rats were exposed to SK609 or PRX and allowed to self-administer the compounds. Rats exposed to SK609 did not acquire self-administration behavior (20 injections for 3 consecutive days), whereas those exposed to PRX reached criterion for reinforcement. Subsequently, these animals were exposed to cocaine and successfully reached self-administration criterion. When switched back to SK609 or PRX, only those exposed to PRX continued to self-administer drug at a high rate, suggesting that PRX demonstrates reinforcing properties, while SK609 has no reinforcing features. These in vitro and in vivo results suggest that compulsive behavior induced by a D3R agonist may be influenced by its biased signaling pathway, which should be considered when evaluating its therapeutic use in neurological disorders.

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Poster

130. Dopamine and Non-Dopamine Pathways in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: Academy of Finland

Jane and Aatos Erkko Foundation

Commission of European Union

Sigrid Juselius Foundation

Title: The analysis of midbrain dopamine system of MANF-deficient mice reveals increased ER stress without phenotypic behavior defects

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Abstract: Chronic endoplasmic reticulum (ER) stress has been connected to development and progression of neurodegenerative diseases, including Parkinson’s disease. ER stress is caused by the accumulation of misfolded and aggregated proteins in the ER. Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a trophic factor, which is involved in the regulation of the unfolded protein response (UPR), a cellular defense mechanism to reduce ER stress. MANF is mainly located in the ER, but is secreted in response to ER stress. It has been shown to protect and restore dopamine neurons in rodent models of Parkinson’s disease, possibly by alleviating ER stress. Interestingly, MANF knockout (KO) mice have chronic ER stress in pancreatic β-cells, which leads to β-cell death and insulin-dependent diabetes. We wanted to study if the lack of MANF causes ER stress also in the brain focusing on dopamine neurons. This study aims to characterize the brain phenotype of MANF conditional knockout (cKO) mice, where MANF has been removed specifically from the central nervous system using Nestin-Cre transgenic mice. In contrast to conventional MANF KO mice, these mice have a normal life-span and do not develop diabetes.
Our results indicate that the UPR induced by ER stress is increased in the brain of MANF cKO mice compared to littermate controls. Since various UPR markers are upregulated in the nigrostriatal dopamine pathway of MANF cKO mice, we wanted to study the survival of dopamine neurons and motor behavior of these mice. The morphology of midbrain dopamine system of MANF cKO compared to control mice is normal. The number of dopamine neurons in substantia nigra and the striatal innervation by dopaminergic neurons remains unaltered in aged MANF cKO mice. Moreover, the expression levels of genes typical for dopamine neurons are

not changed in MANF cKO midbrain compared to controls.
The functional integrity of the midbrain dopamine system was evaluated in locomotor and motor coordination tests. Spontaneous and amphetamine-induced locomotor activities of MANF cKO mice are unaltered compared to controls. We did not find differences between genotypes in motor coordination tests. Moreover, anxiety-like behavior and spatial long-term memory of MANF cKO mice are similar to controls.
We have revealed a mouse model, where neurons have ER stress. However, the chronic ER stress resulted from MANF-deficiency does not affect the maintenance of nigral dopamine neurons or dopamine related motor behavior. Our results of sustained UPR signaling in the MANF cKO brain will be investigated in more detail in brain disease models and *in vitro* in primary neurons from MANF cKO mice.

Disclosures: E. Pakarinen: None. **V. Võikar:** None. **M. Saarma:** None. **M. Lindahl:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.01/T2

Topic: C.03. Parkinson's Disease

Support: R21 NS099862-01

Title: Ultrasound promotes microglial cell ingestion of alpha synuclein and reduces their production of pro-inflammatory substances

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Abstract: Alpha-synuclein (α-syn) is an important pathological target for the neurodegenerative process of Parkinson's disease (PD). While α-syn is an intracellular native protein, it can be deposited into the extracellular space due to, at least two, non-mutually exclusive mechanisms, namely atypical secretion and leakage from healthy and damaged neurons, respectively. Once in the extracellular environment, α-syn is subject to fertilization, oligomerization, and/or modification (nitration, phosphorylation) that can trigger a microglial-derived inflammatory response, and, according to growing number of in vivo and in vitro studies, a "prion-like" cell to cell spreading. We have identified two N9 microglial cell receptors, CD11b and SR-B2 that mediate the ingestion of various forms of α-syn. In addition, we found that microglia ingest the α-syn species (e.g. preformed fibrils [PFFs]) that has been linked to PD less efficiently than those species (e.g. native monomeric α-syn) which has not been linked to PD. Moreover, we noted that opsonization of PFFs enhances N9 ingestion of α-syn as well as the production of key

proinflammatory factors such as TNFα and IL-6. However, when surface acoustic waves (SAW) are applied to N9 cells, the ingestion of opsonized PFFs is enhanced even further while the production of proinflammotory factors, such as IL-6, are dramatically reduced. We thus posit that SAW, by promoting the ingestion of extracellular disease-related proteins like α-syn, will reduce microglia-derived inflammatory response, and may in turn reduce the cell-to-cell transmission of these toxic proteins, and the ensuing neurodegeneration.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: PRIPRIM grant from Michael J Fox Foundation

TARGET PD grant from Agence Nationale de la Recherche

Title: Bidirectional gut-to-brain and brain-to-gut propagation of alpha-synuclein pathology in non-human primates

Authors: *S. DOVERO[1], A. PRIGENT[2], M.-L. AROTCARENA[1], M. BOURDENX[1], P. AUBERT[2], I. TRIGO DAMAS[3], G. PORRAS[1], M.-L. THIOLAT[1], M. TASSELLI[2], F. FERNANDEZ-GOMEZ[4], C. ESTRADA[5], A. RECASENS[6], J. BLESA[3], M. HERRERO[5], M. VILA[6], J. OBESO[3], P. DERKINDEREN[2], B. DEHAY[1], E. BEZARD[1]
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Abstract: The prototypic synucleinopathy Parkinson's disease (PD) is hypothesized to spread out from the enteric nervous system (i.e. the gut) via the vagal nerve up to the central nervous system. Such popular hypothesis is supported by indirect clinical evidences and by experimental data showing gut-to-brain transfer of synucleinopathy using either viral vector delivery of synuclein or recombinant synuclein preformed fibrils.
We here aimed at testing the alternate hypothesis that synucleinopathy can indeed develop upward but also downward, i.e. from the gut to brain and from the brain to the gut. To this end, we used our primate model of synucleinopathy obtained with administration of α-synuclein species contained in PD-derived Lewy bodies (LB) (Recasens et al., 2014). We examined in non-human primates (i) if LB administration in the ventral wall of the stomach (n=5) leads to central nervous α-synuclein aggregation and possibly nigrostriatal degeneration and (ii) if LB

administration in the striatum (n=6) might lead to synucleinopathy into the enteric nervous system of the duodenum.
Two years after injection, extensive analysis was performed to assess qualitatively, quantitatively and spatially in the whole brain and in the enteric nervous system the extent and pattern of lesion as well as the occurrence of synucleinopathy using both biochemical and histochemical procedures. Stomach-LB injected non-human primates showed enteric nervous system pathology and nigrostriatal lesion in keeping with the well-accepted hypothesis. However, striatum-LB injected animals, in addition to the expected nigrostriatal degeneration, showed also enteric nervous system pathology in the duodenum.
This study establishes that α-synuclein species might move up and down the neural axis in non-human primates questioning (i) the hypothesis of a peripheral origin of synucleinopathies (ii) and the specificity of enteric nervous system as biomarkers of PD.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: Michael J Fox Foundation (Project Grant No. 2013-8499)

ANR TargetPD

Title: Variable selection using machine learning to identify new signatures of patient-derived aggregated a-synuclein-induced neurodegeneration in non-human primates

Authors: *M. BOURDENX[1], S. DOVÉRO[1], A. NIOCHE[1], M.-L. AROTCARENA[1], S. CAMUS[1], G. PORRAS[1], M.-L. THIOLAT[1], N. P. ROUGIER[1], A. PRIGENT[2], P. AUBERT[2], S. BOHIC[3], N. KRUSE[4], B. MOLLENHAUER[4], S. NOVELLO[5], M. MORARI[5], I. TRIGO DAMAS[6], M. GOILLANDEAU[1], M. TASSELLI[2], C. PERIER[7], N. GARCIA CARILLO[8], C. ESTRADA[9], A. RECASENS[7], J. BLESA[6], M. T. HERRERO EZQUERRO[9], P.

DERKINDEREN[2], M. VILA[10], J. A. OBESO[11], B. DEHAY[1], E. BEZARD[1]
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Abstract: Emerging evidence strongly suggests that α-synuclein, a major protein component of LB, may be responsible for the spreading of the pathological process within affected individuals. Recently, through an innovative strategy based on the purification of Lewy bodies (LB) containing aggregated α-synuclein from the substantia nigra pars compacta of PD patients, we assessed the prion-like properties of endogenous α-synuclein assemblies in wild-type mice and non-human primates (Recasens et al., Ann. Neurol. 2014). The pilot nature of the demonstration however called for a properly powered demonstration in non-human primates, that we now achieved in a large group of baboons (n=49). After in vitro and in vivo (in mice) LB-induced toxicity validation, α-synuclein-containing LB extracts were injected bilaterally into the striatum. After a live phase of 2 years, extensive analysis was performed using biochemical and histochemical techniques in the whole brain. This study collected over 174 variables in each monkey. To overcome the roadblock associated to the "p>n" problem that occurs when the number of variables measured is greater than the sample size, we developed a multiple layer perceptron (MLP), i.e. an artificial neural network commonly used in machine learning, to assess variable significance. We first distinguished two types of variables: the ones that reflect the actual neurodegeneration - the variables that describe the phenomenon to be explained - and the ones that might contribute to the pathogenic mechanism - the variables that could be useful to explain the phenomenon. We then considered all combinations of 3 variables and used them as input for the MLP. The performance of a given combination of variables was measured to predict the level of degeneration and extract meaningful variables. Variables were then sorted according to their occurrence in the top 1% of the best combinations. Overall, using this unbiased methodology, we confirmed highly-expected variables but, more importantly, also identified unexpected variables that appear to be excellent predictors for dopaminergic neurodegeneration.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Program#/Poster#: 131.04/T5

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson's Disease Research

Title: Optimization of the alpha-synuclein preformed fibril model of synucleinopathy in rats

Authors: *J. PATTERSON[1], C. J. KEMP[1], T. J. COLLIER[4], M. F. DUFFY[2], A. ALLEN[1], K. C. LUK[5], N. M. KANAAN[3], K. L. PAUMIER[6], C. E. SORTWELL[2]
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Abstract: Parkinson's disease (PD) is commonly characterized by the accumulation of alpha-synuclein (α- syn) containing Lewy bodies, progressive neurodegeneration of the nigrostriatal system, and motor deficits. Neurotoxicant, genetic, and viral vector PD models have limited ability to recapitulate all of these key features of PD. We have previously reported that intrastriatal injection of sonicated α-syn preformed fibrils (PFFs) into rats results in widespread α-syn pathology and progressive bilateral nigrostriatal degeneration (≈40%). The present series of experiments explored the impact of modifying various α-syn PFF surgical parameters with the intent of further increasing nigrostriatal degeneration in the rat. Male Fisher 344 rats were used for all studies. Novel striatal coordinates were used to specifically target nigrostriatal terminals in order to seed phosphorylated α-syn inclusions in the substantia nigra pars compacta (SNpc) specifically and to avoid the seeding of inclusions in the ventral tegmental area (VTA). Two different quantities of sonicated mouse α-syn PFFs (8 vs.16 µg) were injected unilaterally into the striatum and compared to α-syn monomer or vehicle control. Lastly, sonicated mouse α-syn PFFs were injected bilaterally into the dorsal striatum. Post-mortem tissue was evaluated using immunohistochemical methods at 2, 4, and 6 months after surgery. Placement of PFFs into the dorsal striatum resulted in a significantly higher percentage of α-syn inclusions within SNpc neurons (>90%, $p = 0.0125$). Rats injected with 16 µg of sonicated mouse α-syn PFFs possessed significantly more nigral α-syn inclusions at the 2-month time point compared to rats injected with 8 µg (2-3 fold increase, $p = 0.0135$). Survival of SNpc dopamine neurons will be quantified and correlated with rat forelimb performance and distance travelled in the open field. Refinements of the rat α-syn PFF model will improve this platform and provide a reproducible synucleinopathy model in which to study pathogenic mechanisms and vet potential neuroprotective therapies.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: Udall Center at the University of Pennsylvania NIH Grant NS 053488

the Michigan State University Neuroscience Graduate Program NIH Grant T32 NS44928

Department of Translational Science and Molecular Medicine

Title: Neuroinflammation precedes nigral degeneration in the alpha-synuclein preformed fibril model of Parkinson's disease

Authors: *M. F. DUFFY[1,2], T. J. COLLIER[2], K. C. LUK[3], M. G. TANSEY[4], K. L. PAUMIER[5], D. FISCHER[2], N. POLINSKI[6], C. J. KEMP[2], C. E. SORTWELL[2]
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Abstract: It remains unclear whether neuroinflammation contributes to nigral degeneration in Parkinson's disease (PD) or is merely a secondary consequence of degenerating neurons. Our lab recently characterized the accumulation of phosphorylated α-syn (pSyn) intraneuronal inclusions and bilateral nigrostriatal degeneration following intrastriatal injection of sonicated α-syn preformed fibrils (PFFs) into rats. To examine the neuroinflammatory signature in this model, male Fischer344 rats received unilateral intrastriatal injections of mouse α-syn PFFs or vehicle (PBS). Cohorts of rats (total n= 90) were euthanized at monthly intervals up to 6 months. pSyn inclusions in the SNpc were most abundant at months 1, 2 and 3, peaking at month 2, with all three time points exhibiting significantly higher α-syn inclusions compared to months 4, 5 and 6 ($p \leq 0.001$). We observed significant, bilateral reduction (~35%) in SNpc THir neurons compared to controls at months 5 and 6 ($p < 0.03$). At 2 months, increases in microglial soma size and in both thickness and number of microglial processes was observed in the SN of PFF injected rats. Major histocompatibility complex-II immunoreactive (MHC-IIir) microglia were observed in the ipsilateral SN in both α-syn PFF and PBS control rats at all time points.

Significantly higher numbers of MHC-II-ir microglia were observed in the SN of α-syn PFF-injected rats compared to control rats at months 2, 4 and 5 ($p < 0.006$) with the highest number of MHC-IIir microglia observed in the SN 2 months following α-syn PFF injection ($p < 0.02$, compared to all other PFF time points), corresponding to the time point when the greatest number of SNpc neurons possess α-syn aggregates. In contrast, significantly fewer MHC-II-ir microglia were observed at months 5 and 6, the interval of SNpc neuron loss. A strong correlation between number of MHC-IIir microglia and the number of SNpc neurons possessing α-syn inclusions was observed ($r^2 = 0.96$). Our results suggest that α-syn PFF seeded synucleinopathy triggers disturbances in local microglia months prior to loss of THir neurons and suggest that reactive microglia may contribute to vulnerability of SNpc neurons to degeneration.

Disclosures: **M.F. Duffy:** None. **T.J. Collier:** None. **K.C. Luk:** None. **M.G. Tansey:** None. **K.L. Paumier:** None. **D. Fischer:** None. **N. Polinski:** None. **C.J. Kemp:** None. **C.E. Sortwell:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.06/T7

Topic: C.03. Parkinson’s Disease

Title: The Michael J. Fox Foundation's efforts to generate, characterize, and promote the use of a variety of preclinical models of Parkinson's disease

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Abstract: Preclinical models are important tools for investigating the pathogenesis and potential therapeutic strategies for diseases like Parkinson’s disease (PD). As the precise etiology of PD is currently unknown and appears to vary among individuals, numerous preclinical models are available to study this disease. To ensure the research community has access to well-validated models of PD, The Michael J. Fox Foundation (MJFF) has taken an active role in designing, validating, and distributing various models of PD that rely on different genetic or interventional manipulations that can be used to investigate mechanisms of PD neurodegeneration or strategies

for preventing, slowing, or halting disease progression. Here we summarize MJFF-led efforts to develop and validate three different types of PD preclinical models: the alpha-synuclein pre-formed fibril (aSyn PFF) model, an aSyn knockdown model using viral vectors, and genetic models of PD. We will include information on the three species of aSyn monomers for PFF generation that MJFF has developed, as well as data validating the toxicity of these PFF species and best practices for generating and validating aSyn PFFs for use in *in vitro* or *in vivo* models. Data will also be presented from validation studies investigating the MJFF-generated aSyn knockdown viral vectors that specifically target mouse or human wildtype aSyn (in addition to common mutant forms of aSyn). In addition, we will highlight MJFF-led efforts to provide the PD research community with more information on different preclinical models available. These efforts include a partnership with www.Alzforum.org to create a PD research models database, as well as a new resource on the MJFF webpage that provides information on MJFF-led efforts to characterize and provide well-validated preclinical models of PD. Ultimately, MJFF's investment in providing the research community with robust, well-characterized animal models and information on choosing an appropriate model will hopefully lead to advancements in PD research.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.07/T8

Topic: C.03. Parkinson's Disease

Support: NHMRC Grant 1100441

Title: Aggregated alpha-synuclein induces cell death via a lysosome-dependent mechanism

Authors: *S. J. GUINEY, P. A. ADLARD, A. I. BUSH, D. I. FINKELSTEIN, S. AYTON
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Abstract: Background: Neuron loss causes symptoms and ongoing progression of Parkinson's disease. Alpha-synuclein is genetically and pathologically linked to Parkinson's disease and is widely considered the disease-causative protein, however, the cell death pathway underlying neurodegeneration remains unknown.
Objective: To identify the cell death pathway activated by aggregated alpha-synuclein in Parkinson's disease.
Methods: Potential cell death pathways involved in alpha-synuclein-induced neurodegeneration were investigated using pre-formed fibrils of alpha-synuclein in cell culture models, with

inducers and inhibitors of cell death pathways with links to Parkinson's disease pathology screened within these models. Toxicity of alpha-synuclein was assessed in multiple immortalised and primary culture cell lines (C57Bl/6/129sv mouse primary cortical neurons, STHdhQ7/7 cells and SN4741 dopaminergic cells), with alpha-synuclein pre-formed fibrils co-administered to cells with modulators of different cell death pathways. Markers characteristic of specific cell death pathways were measured in the intoxicated cells.
Results: Broad-spectrum caspase inhibitors (e.g. Q-VD-OPh) did not recover loss of cell viability due to fibril administration, and preventing activation of necroptosis (e.g. 7-Cl-O-Nec-1) also failed to protect cells. Ferroptosis inhibitors (ferrostatin-1, deferoxamine, reduced-glutathione) failed to rescue the toxicity of alpha-synuclein fibrils, and induction of ferroptosis with glutathione depletion (buthionine sulfoximine) did not exacerbate alpha-synuclein-induced cell death. Activators of autophagic cell death (rapamycin, lithium and valproic acid) did not affect alpha-synuclein-mediated cell death, and alpha-synuclein treated cells did not exhibit changes in autophagy markers (LC3-II/I, p62, ferritin). However, the cell death induced by alpha-synuclein was abolished by lysosomal inhibitors, chloroquine, bafilomycin A1, leupeptin and E64d.
Conclusion: Aggregated alpha-synuclein activated cell death via a lysosome-dependent pathway, independent of autophagy induction. Lysosomal inhibitors could be compounds with potential to protect against neurodegeneration caused by aggregated alpha-synuclein.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation Target Validation Grant

Michael J. Fox Foundation Target Validation Grant

NIH/NINDS P20 NS092530

Title: Peripheral monocyte entry is required for alpha-synuclein induced inflammation and neurodegeneration in a model of Parkinson disease

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Abstract: Accumulation of alpha-synuclein (α-syn) in the central nervous system (CNS) is a core feature of Parkinson disease (PD) that leads to activation of the innate immune system, production of inflammatory cytokines and chemokines, and subsequent neurodegeneration. Here, we used heterozygous reporter knock-in mice in which the first exons of the fractalkine receptor (CX3CR1) and of the C-C chemokine receptor type 2 (CCR2) are replaced with fluorescent reporters to study the role of resident microglia (CX3CR1+) and infiltrating peripheral monocytes (CCR2+), respectively, in the CNS. We used an α-syn mouse model induced by viral over-expression of α-syn. We find that *in vivo*, expression of full-length human α-syn induces robust infiltration of pro-inflammatory CCR2+ peripheral monocytes into the substantia nigra. Genetic deletion of CCR2 prevents α-syn induced monocyte entry, attenuates MHCII expression and blocks the subsequent degeneration of dopaminergic neurons. These results demonstrate that extravasation of pro-inflammatory peripheral monocytes into the CNS plays a key role in neurodegeneration in this model of PD synucleinopathy, and suggest that peripheral monocytes may be a target of neuroprotective therapies for human PD.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: MJFF TARGET VALIDATION

GSRT, SCIENTIFIC EXCELLENCE AWARD

Title: Activin-A mediated suppression of inflammatory responses protects against fibrillar α-Synuclein-induced pathology in the CNS *In vivo*

Authors: M. KARAMPETSOU[1], M. SEMITEKOLOU[2], E. EMMANOUILIDOU[1], J. MORIANOS[2], E. KAPAKI[4], O. EL AGNAF[5], *K. VEKRELLIS[3,5], G. XANTHOU[2]
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Abstract: Parkinson's disease (PD) is characterized by accumulation of misfolded α-Synuclein, deposited mainly within neurons (Lewy Bodies and Lewy neurites), accompanied by progressive loss of dopamine neurons in the Substantia Nigra pars compacta (SNpc). Released α-Synuclein has been proposed to trigger inflammatory responses thus affecting neuronal homeostasis in the context of PD pathogenesis and progression. Neuroinflammation, characterized by activated microglia and infiltrating T cells, is recognized as a key regulator of pathological changes in many neurodegenerative diseases. Activin-A is a pleiotropic cytokine that exerts neuroprotective and anti-inflammatory functions in brain injury models. However, its effects on fibrillar α-Synuclein-induced pathology in vivo remain elusive. As a model of PD-like pathology, Here, we used intrastriatal stereotaxic injections of pre-formed wt α-Synuclein fibrils (PFF) in wt mice to model PD pathology. 2 months post-injection we were able to detect intraneuronal pathological accumulations of phosphorylated α-Synuclein mainly in the midbrain and the cortex.
In vivo therapeutic administration of activin-A in these mice resulted in a significant decrease of α-Synuclein pathological accumulations both in the SNpc and the cortex of the injected animals.Flow cytometry analysis revealed significantly increased frequencies of CD45-GFAP+ astrocytes, accompanied by decreased numbers of CD45+CD11b+ infiltrating macrophages, and CD45+CD11b+Ly6C+ inflammatory myeloid cells, in the cortex and striatum following activin-A administration. Moreover, activin-A inhibited pro-inflammatory TNF-α and increased anti-inflammatory IL-10 cytokine release in the periphery of injected animals, further supporting the notion that activin-A exerts anti-inflammatory functions in mice injected with the PFF. In addition, IFN-γ levels were found significantly reduced in the serum of PFF/activin-A animals, further supporting a neuroprotective role of this cytokine. Interestingly, in vivo neutralization of the endogenous activin-A resulted in exacerbated inflammatory responses in PFF injected mice. Notably, activin-A levels were also measured in the CSF of PD patients and found to be significantly decreased compared to healthy controls.
Together our results demonstrate that activin-A exerts protective functions in PFF-mediated pathology, associated with decreased inflammatory responses in the brain and the periphery and highlight activin-A as a novel immunosuppressive target for the treatment of PD patients.
These studies were funded by a Michael J. Fox Foundation Target Validation Grant Award to KV and GX.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Program#/Poster#: 131.10/T11

Topic: C.03. Parkinson’s Disease

Support: MIUR Young Faculty Program Rita Levi Montalcini

BioSNS Scuola Normale Superiore

Title: Gastrointestinal dysfunction and alpha-synuclein inclusions in enteric neurons precede neurodegeneration in the central nervous system in a mouse model of alpha-synucleinopathies

Authors: *L. ROTA, C. RIZZI, S. CAPSONI, G. TESTA, A. CATTANEO, E. COLLA
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Abstract: Together with typical motor dysfunction, Parkinson's Disease (PD) patients experience a variety of non-motor symptoms that involve both the central (CNS) and peripheral nervous systems with a deep impact on their quality of life. Among those, gastrointestinal (GI) dysfunction and hyposmia can precede even by decades the onset of the motor abnormalities. By affecting up to 80% of PD patients, constipation represents the most frequent GI dysfunction. However very little is known about the relationship between constipation and development of PD.

The aim of this work is to evaluate whether constipation precedes the onset of α-synuclein (αS) pathology and neurodegeneration within the CNS in a genetic model of α-synucleinopathies, the PrP human A53T αS transgenic (Tg) mice. This model develops adult-onset neurodegenerative disease starting after 9 months of age with a progressive motor dysfunction leading to death within 14-21 days. Diseased mice present pathological accumulation of phosphorylated and aggregated αS in the CNS, absent at presymptomatic stages.

Behavioural analysis of constipation in presymptomatic mice showed persistent GI dysfuction in Tg mice already at 3 months of age. Specifically, compared to age-matched controls, the whole gut transit time of Tgs was about 2 hours slower at 3 months and increased to a 4 hours delay by 6 months. Although the consistency and total stool amount were unchanged, the number of pellets produced decreased in presymptomatic Tg mice, suggesting a deficit in propulsive and contractile movements rather than food malabsorption.

The analysis of expression of αS transgene in the mouse intestine showed accumulation of soluble and insoluble αS predominantly in the colon starting at 3 months of age. Interestingly also endogenous mouse αS expression was confined to the colon in Tg and wild-type mice. Insoluble αS was found aggregated and phosphorylated at serine 129 in the colon of presymptomatic mice and localized within neurons of the myenteric and submucosal plexi of the enteric nervous system (ENS). To a lesser extent we found high molecular weight and phosphorylated αS species in the soluble fraction of young Tg mice, suggesting overall that pathological changes associated with αS toxicity appear in the ENS well before the CNS.

These data demonstrate that PrP human A53T αS Tg mice develop significant GI abnormalities accompanied by accumulation of αS aggregates in the ENS of the colon several months before the onset of neurodegeneration, αS inclusions formation in CNS, and onset of the motor phenotype. We conclude that this model can be useful to study early peripheral changes in αS pathology before overt CNS neurodegeneration.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: NIH Grant R01NS064934-07

NIH Grant R21NS097643-01

Title: Biophysical characteristics of α-synuclein fibrils that dictate inclusion formation and neurodegeneration

Authors: *N. BRYANT, H. ABDELMOTILIB, T. MALTBIE, V. DELIC, A. B. WEST
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Abstract: Lewy body diseases (LBDs) involve the spread of α-synuclein inclusions, composed primarily of α-synuclein fibrils, across much of the brain in Parkinson disease, Lewy Body Dementia, Multiple System Atrophy, and Alzheimer disease. Exposure of rodent brain tissue to pre-formed α-synuclein fibrils created from recombinant protein or isolated from inclusions in brains with neurodegenerative disease can result in the corruption of endogenous α-synuclein into additional fibrils in neurons. We have found that the development of inclusions and their spread in the brain correlates with neurodegeneration. However, the fate of fibrils immediately after injection is not clear as basic aspects like diffusion and turn-over have not been previously reported. Further, whether the injected material itself forms some types of inclusions later detected in neurons with antibody approaches is also unclear. Here, we describe how fibrils spread in the brain after initial injection, how they turn over, and what types of cells internalize the fibrils to later form inclusions. We focus on how fibril length might affect these characteristics and how local turn-over and uptake selectively dictate vulnerability to inclusion formation and neurodegeneration. Through these studies, we hope to bridge biophysical characteristics of α-synuclein fibrils together with neurodegenerative phenotypes in the brain.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: MEXT/JSPS KAKENHI Grant Number JP 15K09315

Title: Oxidative modification of α-synuclein by dopamine induces cellular vulnerability and secretion of α-synuclein

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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the selective loss of dopamine (DA) neurons and the presence of Lewy bodies. Furthermore, prion-like propagation of α-synuclein (α-syn) has also been paid attention recently. However, it is not well understood why PD-related pathogenesis including cell vulnerability and propagation of α-syn occurs in selective neurons. To clarify the effect of DA on secretion and toxicity of α-syn, we investigated the interaction between DA and α-syn protein. We generated PC12 cells expressing human α-syn, as well as the several mutants in a tetracycline-inducible manner. Using these cell lines, we investigated cell viability, oxidized methionine (Met(O)) in α-syn, degradation and/or secretion of α-syn under DA metabolism. We also investigated the effects of Met(O) in α-syn induced by DA on α-syn-related toxicity and stability of α-syn. Overexpression of wildtype α-syn decreased cell viability, while an inhibitor of tyrosine hydroxylase (TH) blocked this vulnerability, suggesting that α-syn-related cytotoxicity is associated with DA metabolism. The vulnerabilities of mutant (M127A) cell line was lower than that of wildtype α-syn-expressing cells. Moreover, α-syn containing DA-mediated oxidized methionine (Met(O)) was detected in our cell lines. In these cell lines, intracellular level of α-syn was controlled by autophagic/lysosomal degradation and by secretion to extracellular space. TH-inhibitor or M127A mutation of α-syn decreased intracellular degradation and secretion of α-syn. Our results suggest that M127 is the major target for oxidative modification by DA, and this modification is associated not only cell vulnerability but also intracellular stability and secretion of α-syn in the pathogenesis of PD.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.13/U2

Topic: C.03. Parkinson's Disease

Title: Dopal-treated α-synuclein disturbs mitochondrial membrane potential

Authors: *J. B. WATSON, G. SEROBYAN, A. YACOUB, A. KUNZ, J. P. WHITELEGGE, T. A. SARAFIAN
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Abstract: The α-synuclein protein exists in a variety of aggregated proteoforms associated with Parkinson's disease (PD) pathology. We previously reported that α-synuclein can disturb both mitochondrial function (Sarafian et al., 2013, PLoS One 8(5):e63557) and presynaptic neurotransmitter release (Sarafian et al., 2016, DOI: 10.1002/jnr.24024). The latter effect was based on altered glutamate release in a synaptoneurosome preparation and was enhanced by fibrillated forms of recombinant human α-synuclein. Among the various structural variants of α-synuclein, amyloid oligomers are believed to be the most neurotoxic. For example, it has been reported that dopamine and its intraneuronal metabolite, 3, 4-dihydroxyphenylacetaldehyde (DOPAL) promote formation of oligomeric/protofibrillar α-synuclein structures and interfere with fibril formation (Conway et al., 2001, DOI: 10.1126/science.1063522; Plotegher et al., 2017, DOI: 10.1038/srep40699). We have now observed that fibrillation of α-synuclein in the presence of dopamine or DOPAL greatly enhanced formations of higher molecular weight oligomers of α-synuclein, whereas oxidation of α-synuclein with Cu^{2+}/H_2O_2 did not. Functional studies using isolated mouse forebrain mitochondria revealed that DOPAL-treated α-synuclein produced the greatest toxic effects on mitochondrial membrane potential compared with dopamine-treated or Cu^{2+}/H_2O_2-treated α-synuclein. The results suggest that brain cells containing dual high levels of DOPAL and α-synuclein, such as those in substantia nigra's pars compacta, may be selectively vulnerable to injury and death in PD. Overall the studies support the hypothesis that DOPAL-mediated structural modification of α-synuclein may be a key mechanism underlying PD neuropathology.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: Munich cluster for systems neurology (SyNergy) grant EXZ1010

Title: Relevance of different alpha-Synuclein species in Parkinson's disease

Authors: *T. CHAKROUN[1], T. W. RÖSLER[1], M. HÖLLERHAGE[1,2], G. U. HÖGLINGER[1,2]
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Abstract: Understanding the role of alpha-synuclein (αSyn) in Parkinson's disease and other synucleinopathies is crucial to develop sucessful disease-modifying strategies. Immunotherapy with αSyn-targeting antibodies is considered one of the most promising approaches to block αSyn spreading. The key prerequisite for safe and efficient immunotherapy is to target specific αSyn species with well-defined epitopes. These species need to be pathologically relevant in terms of spreading and toxicity, and readily accessible for therapeutic antibodies.
In order to identify such species, we analyzed the conditioned medium from human postmitotic dopaminergic neurons (LUHMES neurons). Interestingly, we found that cells challenged by αSyn overexpression respond by releasing specific αSyn species in the medium. These secreted species were separated from conditioned medium by continuous elution electrophoresis. Additionally, tandem mass spectrometry was applied to determine their molecular identity.
Our findings led us to systematically study the effects of various predefined recombinant αSyn species. We studied their release, uptake, seeding capacity and toxicity in LUHMES neurons. Using a wide range of techniques, we were able to identify two pathologically relevant species that may be used as particularly promising therapeutic targets. Species of interest were taken up readily by cultured neurons. In addition, each of them induced different aggregation patterns of αSyn. Intriguingly, each aggregation pattern was only detectable by specific antibodies. This further suggests that these two species may lead the aggregation of endogenous αSyn into specific pathways, making them strong candidates for triggering the formation of different αSyn strains. This also shows the importance of selecting the right epitopes for immunotherapy.
In summary, our preliminary results show that specific αSyn species are released from neurons overexpressing wild-type αSyn, induce aggregation of endogenous αSyn and may lead αSyn aggregation into specific pathways with distinct pathological 'footprints'. Hence, we hypothesize that the formation of these specific species is an upstream and essential disease related mechanism, thus making them very promising targets for immunotherapy.

Disclosures: **T. Chakroun:** None. **T.W. Rösler:** None. **M. höllerhage:** None. **G.U. Höglinger:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Title: Trehalose acts as autophagic flux inhibitor and promotes a-synuclein aggregation and secretion

Authors: *Y.-S. YOON
Konkuk Univ., Seoul, Korea, Republic of

Abstract: Autophagy, the process of protein degradation and organelle turnover, contributes to maintain cellular homeostasis, and is critical in a wide range of normal human physiological processes. Dysregulated autophagy result in failure of the degradation of impaired organelles and accumulation of protein aggregates, which are the characteristics of many neurodegenerative diseases. Previous studies show that non-reducing disaccharide trehalose induce autophagy and has received high attention for its beneficial effects in different disease models of neurodegeneration. However, how trehalose promotes autophagy has not been fully revealed. Here we investigated the effect of trehalose and other disaccharide on autophagic flux and Parkinson's disease.
Treatment of trehalose on differentiated human neuroblastoma cells or rat primary cortical neuron culture resulted in the accumulation of autophagy marker (LC3II), substrate protein (p62) and autophagosomes, while it decreased number of autolysosomes and the permeability increased indicating membrane perturbation of lysosomes. Furthermore in α-synuclein overexpressed cells treated with trehalose displayed increased a-synuclein aggregation. The amount of a-synuclein in the culture medium was also elevated which indicate increased cell-to-cell transmission of a-synuclein. Despite the substantial increase in a-synuclein aggregation, which normally leads to cell death, cell viability was not affected upon treatment with trehalose, suggesting an autophagy-independent protective function of trehalose against protein aggregates. These results suggest that although trehalose has been widely considered an autophagic inducer, it may be actually a potent blocker of autophagic flux.

Disclosures: Y. Yoon: None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Title: Striatal seeding of protofibrillar alpha-synuclein leads to neuronal hyperactivity and coincide with a reduction of GAD67-positive cells in the somatosensory mouse cortex

Authors: C. SGOBIO[1], S. BLUMENSTOCK[1,2,3], F. SUN[1], M. M. DOROSTKAR[1,2], J. HERMS[1,2,3]
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Abstract: Aggregates of alpha-synuclein (a-Syn) protein are considered the main hallmark of synucleinopathies, such as Parkinson's disease, multiple system atrophy and dementia with Lewy bodies. Abundancy of extracellular levels of a-Syn critically promotes the onset of neurodegenerative processes. This observation arises from a-Syn propagation in animal model studies as well as clinical reports demonstrating that healthy neuronal grafts transplanted into PD patients often degenerate. Recently, we showed that both overexpression and seeding of wild-type a-Syn in mice affects cortical dendritic spine density and impairs structural plasticity in an age-dependent manner (Blumenstock et al. EMBO Mol. Med. 2017). Presently, we performed striatal inoculation of a-Syn fibrils to induce cortical a-Syn pathology. After 9 months, we monitored calcium transients by in vivo two-photon microscopy, reporting an increase of cortical neuronal activity on top of the previously described structural impairments. The observed increase in amplitude and frequency of calcium transients concurred with a significant decrease of GAD67-positive cortical interneurons, estimated by unbiased stereological quantification along the somatosensory (SSp) cortex. These data sustain the hypothesis that the spreading of elevated level of extracellular a-Syn alters the excitatory-inhibitory balance in cortical circuits, possibly triggering the dendritic spine pathology underlying synucleinopathies.

Disclosures: C. Sgobio: None. **S. Blumenstock:** None. **F. Sun:** None. **M.M. Dorostkar:** None. **J. Herms:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.17/U6

Topic: C.03. Parkinson's Disease

Support: CIHR Grant

Title: On the mechanism of internalization, trafficking and release of alpha synuclein in cellular models of Parkinson's disease

Authors: *L. RODRIGUEZ, M. MARANO, M. S. FRASER, J. WATTS, A. TANDON
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Abstract: Emerging evidence suggests that amyloid-like fibrils composed of misfolded proteins propagate throughout the brain in many neurodegenerative diseases including Parkinson's disease (PD). Recent studies have shown that alpha-synuclein (a-syn), the main component of Lewy bodies in PD, can be released from neurons and propagate from cell-to-cell in a prion-like manner. However, the mechanism of uptake and release of misfolded and/or aggregated a-syn is still not completely understood. We investigated the cellular mechanism underlying a-syn fibrils uptake, trafficking and release in different cell models including human embryonic kidney cells (HEK 293) stably expressing the A53T a-syn mutant and mouse cortical neurons. Exogenous a-syn fibrils are efficiently internalized by endocytosis and degraded within the endo-lysosomal system. Labelled fibrils localized to late endosomal compartments and to multivesicular bodies (MVB), which seem to serve as intermediate compartment for sorting of a-syn towards lysosomes for degradation or the plasma membrane for its release. We also tested the hypothesis of exocytosis as an alternative mechanism for protein homeostasis by inhibiting a-syn degradation and studying its trafficking and release. Better understanding of the mechanism of intra and inter-cellular trafficking of a-syn is of crucial importance for understanding its pathogenesis and for developing new treatments for PD.

Disclosures: L. Rodriguez: None. **M. Marano:** None. **M.S. Fraser:** None. **J. Watts:** None. **A. Tandon:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Program#/Poster#: 131.18/U7

Topic: C.03. Parkinson's Disease

Support: NSF Award 1523620

NIH-NIMDH Grant 4U54MD008621-04

Title: *In vitro* compartmentalization accelerates the formation of toxic alpha synuclein protein aggregates

Authors: D. L. CASTILLO[1], S. TATE[1], K. INGRAM[1], L. RICKS-SANTI[1], *M. J. GUERRERO[2]
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Abstract: Alpha synuclein (αS) is a protein usually located in the membrane of presynaptic vesicles. In Parkinson's disease (PD), this protein plays a toxic role when adopt amyloid conformations. αS is detected in monomeric and multimeric conformations, however only β-sheet rich structures are related to pathological states. The cause triggering αS aggregation in sporadic PD remains elusive. A recent study using distinct αS mutants suggest that conditions breaking the balance of αS distribution in the cell is enough to trigger the formation of toxic aggregates. In this study, we evaluated the effects of *in vitro* compartmentalization in a crowded system containing wild type αS. Here we found that αS is distributed in two distinct compartments however the protein contained in each compartment display distinct aggregation and toxic properties in neuronal cell cultures. Furthermore, experiments where compartmentalization was induced and reversed showed accelerated αS aggregation compared to experiments where compartmentalization was not induced. These results suggests that local intracellular changes could trigger the formation of toxic aggregates that further induce the aggregation of normal αS aggregation.

Disclosures: D.L. Castillo: None. **S. Tate:** None. **K. Ingram:** None. **L. Ricks-Santi:** None. **M.J. Guerrero:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Support: KBRI Grant 17-BR-02

Korea NRF-2013R1A1A3012721

Title: Specific protein sequestration effect of alpha-synuclein aggregates leads neurovascular unit impairment

Authors: *W. OH, D.-G. KIM, M.-J. KIM, R. YU, M.-G. CHOI
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Abstract: α-Synuclein (α-Syn) is a major component of Lewy bodies found in synucleinopathies including Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB). Under the pathological conditions, α-Syn tends to generate a diverse form of aggregates showing toxicity to neuronal cells and able to transmit across cells. However, unlike amyloid beta which is the causative agent of Alzheimer's disease (AD), the pathogenic effect of α-Syn on neurovascular unit (NVU) is not fully elucidated. In this study, we found that α-Syn aggregates, globular shape and resistant to SDS, preferentially sequester specific cellular proteins through direct binding in the cell-free system as well as PD mouse model. This direct sequestration mechanism by which α-Syn aggregates affect cytotoxicity in neurovascular unit cells such as neurons as well as endothelial cells. We also observed physiological dysfunction such as permeability changes in the α-Syn-treated brain endothelial cells. Moreover, *in vivo* administration of α-Syn induces disruption of physiological function and integrity of NVU suggesting that α-Syn aggregates possibly involved in progression of PD pathological sign.

Disclosures: W. Oh: None. **D. Kim:** None. **M. Kim:** None. **R. Yu:** None. **M. Choi:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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

EC Joint Programme on Neurodegenerative Diseases (JPND-NeuTARGETs-ANR-14-JPCD-0002-02)

France Parkinson Foundation

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Title: *In vitro* and *Ex vivo* assesment of the role of astrocytes in alpha-synuclein spreading

Authors: *F. LORIA[1], J. Y. VARGAS[1], S. SYAN[1], L. BOUSSET[2], R. MELKI[2], C. ZURZOLO[1]
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the formation of intracellular inclusions mainly composed of α-synuclein (α-syn) aggregates. Recent evidence suggests that PD progression could occur by intercellular spreading of α-syn aggregates throughout the brain in a prion-like manner. However, the mechanisms and cellular types responsible for this intercellular propagation are not yet fully elucidated. While the pathological manifestations of PD are mainly observed in neurons, it is not clear yet if astrocytes may also contribute to the propagation of proteinaceous aggregates, as recently suggested for other neurodegenerative disorders. Here we studied the role of astrocytes on the intercellular transfer and fate of aggregated α-syn fibrils, using *in vitro* and *ex vivo* models. We found that α-syn fibrils can be transferred to neighboring cells, however the transfer efficiency changes depending on the cellular types. Indeed, we observed that α-syn is efficiently transferred from astrocytes-to-astrocytes and from neurons-to-astrocytes, but not from astrocytes-to-neurons. Interestingly, α-syn puncta are mainly found inside the lysosomal compartments of the recipient cells. However, differently from neurons, astrocytes are able to efficiently degrade fibrillar α-syn, suggesting an active role for these cells in clearing α-syn deposits. We also found that α-syn can be transferred from astrocytes to naive hippocampal slices, in a way that involves almost exclusively astrocyte-to-astrocyte transmission. Finally, we observed that astrocytes co-cultured with organotypic brain slices are able to take up α-syn fibrils from the slices. Altogether our data support a role for astrocytes in trapping and clearing α-syn pathological deposits in PD.

Disclosures: F. Loria: None. **J.Y. Vargas:** None. **S. Syan:** None. **L. Bousset:** None. **R. Melki:** None. **C. Zurzolo:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: C.03. Parkinson's Disease

Support: NIH/NINDS Grant R01NS082565

Title: Analysis of neuropathology in Pink1 knockout rats induced by Alpha-synuclein preformed fibrils

Authors: *R. B. CREED[1], M. S. GOLDBERG[2]
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Abstract: Alpha-synuclein-immunoreactive pathology is one of the main pathological hallmarks of Parkinson's disease (PD). Mutations in the alpha-synuclein gene are causally linked to dominantly inherited forms of PD and mutations in the PTEN-induced putative kinase-1 (PINK1) gene are linked to recessively inherited forms of PD. PINK1 knockout (KO) rats develop alpha-synuclein-immunoreactive pathology in addition to locomotor deficits and age-dependent loss of dopaminergic neurons in the substantia nigra pars compacta. Because abnormal alpha-synuclein protein aggregates appear spontaneously in PINK1 KO rats around the same age that neurodegeneration begins, we hypothesize that PINK1 KO rats are more prone to alpha-synuclein aggregation compared to wild-type (WT) rats. We further hypothesize that induction of alpha-synuclein aggregation can accelerate neurodegeneration in PINK1 KO rats compared to WT controls. To test these hypotheses, we injected alpha-synuclein pre-formed fibrils (PFFs) or alpha-synuclein monomer into the striatum of PINK1 KO and WT control rats at age three months, prior to the appearance of significant pathology in PINK1 KO rats. Four weeks post-injection, animals were perfused and brains were removed, cryoprotected, and serially sectioned in the coronal plane. Systematically spaced sections were stained by immunofluorescence using antibodies specific for serine 129-phosphorylated (pS129) alpha-synuclein as a selective marker for aggregated alpha-synuclein, and antibodies specific for tyrosine hydroxylase (TH) as a marker for dopaminergic neurons. We measured total pS129 alpha-synuclein immunoreactivity in various brain regions including the substantia nigra. Additionally, we measured the number of cells immunoreactive for both pS129- alpha synuclein and TH in the substantia nigra as a percentage of the total number of TH cells in the substantia nigra. These studies are important for defining the role of alpha-synuclein aggregation in PD pathogenesis and for determining the extent to which pS129 alpha-synuclein causes or accelerates neurodegeneration in PINK1 KO rats.

Disclosures: R.B. Creed: None. **M.S. Goldberg:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Program#/Poster#: 131.22/U11

Topic: C.03. Parkinson's Disease

Support: Marie Sklodowska-Curie grant agreement No 641805

Title: Development of Visual Assay for Detection of α-synuclein Spreading; a rat model of α-synuclein pathology

Authors: *F. ØSTERGAARD[1,3,4], A. WADE[3], K. CHRISTENSEN[1], B. LAURSEN[2], H. SIEBNER[4], T. DYRBY[4]
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Abstract: Parkinson's disease (PD) is a neurodegenerative disease traditionally connected to the ablation of dopaminergic cells in the substantia nigra pars compacta (SNc). The Braak hypothesis suggests that spreading of α-synuclein aggregates in the peripheral and central nervous system is a crucial part of the disease. This theory is increasingly supported by data obtained from rodent PD models such as the AAV α-synuclein rat model. Although visual deficits have consistently been described as part of PD symptomatology, only a few study reports of α-synuclein pathology in the visual system exist. Here we study visual processing in the AAV α-synuclein rat model of PD. In our studies, female Sprague-Dawley rats received unilateral injections with AAV containing human SNCA in the SNc. As the visual system and the basal ganglia are connected via the superior colliculus, visual evoked potentials (VEPs), and steady-state VEPs (SSVEPs) were recorded once a week, for ten weeks, from the superior colliculus and the visual cortex of freely moving rats. Effects of α-synuclein pathology are expected to modulate the electroencephalographic responses.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

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Program#/Poster#: 131.23/U12

Topic: C.03. Parkinson's Disease

Title: Single-molecule pull-down assay of alpha-synuclein in dopaminergic neurons of postmortem brain tissue

Authors: G. JE[1], B. CROOP[2], *K. HAN[2], Y.-S. KIM[1]
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Abstract: Quantifying the protein expression level and detecting aberrant proteins are critical to many therapeutic areas. However, it is difficult to detect a small trace of the proteins as contrasted with DNA or RNA, and it is even more challenging to reveal their oligomerization state which is often a hallmark of several neurodegenerative diseases. Single-molecule pull-down (SiMPull) assay is a powerful tool that enables us to directly count the number of single proteins, and reveal the stoichiometry of the protein complex by single-molecule fluorescence microscopy. Here we applied SiMPull assay to elucidate the protein level and the aggregation of α-SYN examined from dopaminergic neurons in the *substantia nigra* of postmortem brain tissue. Our quantitative and ultrasensitive analysis will be highly useful in diagnostic applications using various specimens for neurodegenerative diseases including Alzheimer's disease and Parkinson's disease.

Disclosures: G. Je: None. **B. Croop:** None. **K. Han:** None. **Y. Kim:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: Branfman Family Foundation Grant

l'Agence Nationale de la Recherche (ANR-12-BSV4-001-01-TargetPD)

LabEx BRAIN (E.B. and B.D.)

Title: Effects of A53E substitution on alpha-synuclein aggregation and neurotoxicity in Parkinson's disease models

Authors: *P. C. MONTENEGRO[1], D. YSSELSTEIN[2], N. DUTHEIL[4], S. AGIM[3], B. DEHAY[4], E. BEZARD[4], J. R. CANNON[3], J.-C. ROCHET[2]
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Abstract: Parkinson's disease (PD) is characterized by the presence in post-mortem brains of Lewy bodies with aggregated forms of alpha-synuclein (aSyn), a presynaptic protein that exists as both cytosolic and membrane-bound forms. Neuropathological findings suggest that aggregated species of aSyn are involved in neuronal cell death. However, mechanisms by which aSyn forms neurotoxic aggregates in PD are poorly understood. Data obtained by our group and others suggest that a disruption of interactions between aSyn and phospholipid membranes leads to a shift to an 'exposed' conformation that favors aggregation of the protein at membrane surfaces. To further address this hypothesis, we characterized a new familial PD mutant form of aSyn, A53E, in terms of its propensity to undergo membrane-induced aggregation and elicit neurotoxicity, based on the rationale that the introduction of a negatively charged residue at position 53 could potentially interfere with aSyn-membrane interactions. Circular dichroism analyses revealed that A53E has a weaker affinity for phospholipid vesicles compared to WT aSyn or another familial PD mutant, A53T. Data from 2D-NMR analyses suggested that the A53E substitution modestly perturbs the interaction of the central hydrophobic domain with phospholipid vesicles, and this effect correlated with an increase in the ability of A53E to undergo membrane-induced self-assembly compared to WT aSyn. Additional findings revealed that A53E has a high propensity to trigger the disruption of synthetic vesicles and to elicit dopaminergic cell death in primary midbrain cultures. Current studies are focused on comparing A53E, WT aSyn, and A53T in terms of neurotoxicity and aggregation propensity in a rat rAAV model. Rats injected unilaterally in the substantia nigra with rAAV-aSyn virus or a vector-control virus are now being characterized in terms of various behavioral endpoints. Twelve weeks after the injection, the rats will be euthanized, and their brains will be examined immunohistochemically to assess striatal DA terminal density, nigral DA neuron viability, and aSyn inclusion levels. The results of these studies will yield insights into the molecular basis for the neurotoxicity of A53E and shed light on a potential role for membrane-induced aSyn aggregation in PD pathogenesis *in vivo,* thus setting the stage for developing therapies to slow neurodegeneration in the brains of PD patients.

Disclosures: **P.C. Montenegro:** None. **D. Ysselstein:** None. **N. Dutheil:** None. **S. Agim:** None. **B. Dehay:** None. **E. Bezard:** None. **J.R. Cannon:** None. **J. Rochet:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

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This work benefited from equipment and services from the CELIS cell culture facility, at ICM

Title: Dopamine inhibits glutamate release evoked by alpha-Synuclein aggregates in microglial cells

Authors: *P. P. MICHEL[1], M. DOS SANTOS PEREIRA[1,2], L. ACUÑA[1,3], S. HAMADAT[1], J. ROCCA[1], F. GONZÁLEZ[4], R. CHEHÍN[4], J. SEPULVEDA-DIAZ[1], E. DEL BEL[2], R. RAISMAN-VOZARI[1]
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Abstract: Microglial cells, the resident immune cells of the brain, play a key role in inflammatory-type processes that promote neurodegeneration in Parkinson's disease (PD). The presence of α-synuclein aggregates (ASa) in PD brains may be a trigger for the microglial inflammatory response. Here, our aim was to characterize the impact of ASa on microglial cells, using glutamate release as a marker of the activation state of these cells. For that, we established cultures of microglial cells purified from post-natal mouse pup brains (Sepulveda-Diaz et al, Glia, 2016) and exposed them to ASa prepared as described before (González-Lizárraga et al, Sci Rep, 2017). Conditioned media were collected for glutamate quantification using an ELISA assay kit. Adherent cells were used for either assessment of reactive oxygen species or immunostaining procedures and cell lysates for western blot immunoassays. The modulatory effect of ASa on cystine transport was monitored through a measure of [14C]-L-Cystine accumulation. ASa robustly stimulated glutamate release in microglial cells through a mechanism requiring concomitant activation of TLR-2 and P2X7 receptors and downstream stimulation of PI3K-dependent signaling. The increase in glutamate release and the intensification of oxidative stress associated to it, were prevented by antioxidants, such as Trolox, a vitamin E analog and apocynin, a NADPH oxidase inhibitor. Sulfasalazine, a drug used to treat chronic inflammatory diseases such as rheumatoid arthritis, prevented the release of

glutamate induced by ASa and the concomitant increase in cystine uptake. This suggested that glutamate release induced by ASa was the consequence of the activation of the cystine/glutamate antiporter system Xc-. Most interestingly, the neurotransmitter dopamine (DA) totally prevented the induction of glutamate release induced by ASa through an antioxidant effect that required inhibition of PI3K signaling. Altogether, present data suggest that ASa may participate in PD progression by promoting a toxic build-up of extracellular glutamate and low-level excitotoxic stress. The deficit in DA that characterizes PD may amplify this process in a vicious circle mechanism.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Title: Protective effects of endosulfine-alpha (ENSA) against alpha-synuclein aggregation and neurotoxicity in Parkinson's disease models

Authors: *A. CHANDRAN[1,4], D. YSSELSTEIN[1,4], P. C. MONTENEGRO[2,4], I. COSTANTINO[5], N. DUTHEIL[6,7], G. P. MCCABE[3], M. P. FROSCH[5], J. M. GEORGE[8], B. DEHAY[6,7], E. BEZARD[6,7], J.-C. ROCHET[1,4]
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Bordeaux, Inst. des Maladies Neurodégénératives, UMR 5293, Bordeaux, France; [7]CNRS, Inst. des Maladies Neurodégénératives, UMR 5293, Bordeaux, France; [8]Sch. of Biol. and Chem. Sci., Queen Mary Univ. of London, London, United Kingdom

Abstract: Oligomerization of the presynaptic protein alpha-synuclein (aSyn) is thought to play a key role in the pathogenesis of Parkinson's disease (PD). aSyn interacts with anionic phospholipid vesicles by forming an amphipathic α-helix of various lengths. Evidence suggests that disruption of interactions between aSyn and phospholipid membranes leads to a shift to a short-helix, lipid-bound form, which is more susceptible to the formation of toxic aSyn oligomers due to exposure of the protein's central hydrophobic region. Previously we showed that A30P and G51D, two aSyn variants with disrupted membrane interactions, had an increased ability to form aggregates at the surface of synthetic phospholipid vesicles and to elicit neurotoxicity than wild type (WT) aSyn, and both triggered vesicle disruption under conditions identical to those that promoted membrane-induced aggregation. We hypothesize that interactions between aSyn and other proteins at the membrane surface should prevent lipid-induced aSyn aggregation and alleviate aSyn neurotoxicity. To address this hypothesis, we characterized endosulfine alpha (ENSA), a neuronal protein that interacts selectively with membrane-bound aSyn, in terms of its effects on membrane-induced aSyn aggregation, membrane permeabilization, and neurotoxicity. WT ENSA (but not the non-aSyn binding S109E variant) attenuated aSyn self-assembly at the membrane, vesicle disruption, and aSyn neurotoxicity. Intriguingly, ENSA was found to be down-regulated in the frontal cortex of patients with dementia with Lewy bodies and in the *substantia nigra* of PD patients. Current efforts are focused on examining protective effects of ENSA in a neuronal cell culture model using (i) an in-cell crosslinking approach to monitor intracellular aSyn self-assembly, and (ii) imaging methods to monitor the aSyn-mediated deacidification of intracellular vesicles loaded with a pH-sensitive fluorophore. Additional studies are aimed at characterizing ENSA in terms of its ability to alleviate aSyn neurotoxicity and aggregation in rodent synucleinopathy models. Collectively, our results support the idea that ENSA up-regulation is a viable strategy to alleviate aSyn aggregation and neurotoxicity in PD and other synucleinopathy disorders.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Topic: C.03. Parkinson's Disease

Support: NSERC

SHRF

CFI

Heart and Stroke

Title: Chronic stimulation of adenosine A1 receptor promotes alpha-synuclein aggregation in hippocampal and substantia nigral neurons

Authors: *E. JAKOVA[1], J. STOCKWELL[1], S. NOSIB[1], J. S. LEE[2], F. S. CAYABYAB[1]
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Abstract: Destruction of dopaminergic neurons in substantia nigra pars compacta (SNc) underlies the motor deficits observed in Parkinson's disease (PD). Although various therapeutic strategies are available to alleviate the symptoms of PD, including dopamine replacement therapy and monoamine oxidase inhibitors, none of these therapies slows progression of the disease. Since we recently reported that adenosine contributes to neuronal damage in in vivo and in vitro stroke models, we now hypothesize that aging-related elevation of cerebral adenosine leads to dopaminergic neuron damage in substatia nigra pars compacta. Using male Sprague-Dawley rats, we administered the adenosine A1 receptor (A1R) agonist N^6cyclopentyladenosine (CPA) by intraperitoneal injection, and tested the effects of novel neuroprotective agents in hippocampal and SNc neurodegeneration. Compared to vehicle controls, systemic administration of 3mg/kg CPA for 7 days caused hippocampal-dependent learning deficits (Y-maze test) consistent with increased neurodegeneration of hippocampal neurons (FluoroJade B staining and NeuN labelling). CPA-treated rats also showed significant motor impairment and increased depressive behavior (forced swim test), which was prevented by A1R antagonist DPCPX, 1-aminoindan (a metabolite of Rasagiline), or caffeine-1-aminoindan dimer. In contrast, the amphetamine metabolite 2-aminoindan, which is structurally similar to 1-aminoindan, did not prevent the CPA-mediated behavioral deficits. Using nanopore and imaging analyses, we determined that the neuroprotective compounds exerted their effects by binding directly to the alpha-synuclein and preventing A1R-mediated increase in alpha-synuclein misfolding and aggregation. Taken together, these data suggest that the A1R-alpha-synuclein interaction represents a novel therapeutic target for PD.

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Poster

131. Alpha-Synuclein Aggregation and Transmission

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Program#/Poster#: 131.28/V5

Topic: C.03. Parkinson's Disease

Title: Characterization of 4L/PS-NA mice as alpha-synuclein aggregation model

Authors: *E. AUER, M. FARCHER, R. RABL, V. SCHIFFER, S. FLUNKERT, M. POSCH, B. HUTTER-PAIER
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Abstract: Gaucher disease is the most common lysosomal storage disease. The neuronal disease variant is characterized by aggregated protein accumulations in the brain and associated neurological manifestations. The disease is autosomal recessively inherited and modeled by 4L/PS-NA mice that express low levels of prosaposin and saposins, as well as beta-glucocerebrosidase (GCase) with a point mutation at V394L/V394L. Mutations of GCase are common risk factors for the development of synucleinopathies like Parkinson's disease or dementia with Lewy bodies. To use 4L/PS-NA mice for compound tests against the Gaucher disease or alpha-synuclein aggregation diseases, a detailed characterization of these mice is needed. We thus analyzed 4L/PS-NA mice for their neuropathological features. 4L/PS-NA mice were histologically analyzed for murine alpha-synuclein and GCase expression, neuroinflammation using astroglios and microgliosis marker GFAP and Iba1 as well as ubiquitination. Additionally, animals were analyzed for general health and behavioral deficits using different activity and motor tests. Our results show that 4L/PS-NA mice present with progressively increasing murine alpha-synuclein aggregation levels and strong neuroinflammation. The health and behavioral analysis shows that 4L/PS-NA mice have a lower body weight and temperature as well as motor deficits as analyzed with the wire suspension test. Analysis of 4L/PS-NA mice in the Open Field test revealed a reduced rearing behavior. Our results show that 4L/PS-NA mice present with highly increased alpha-synuclein aggregation, related neuroinflammation as well as physiological and behavioral changes. Since the effect on alpha-synuclein protein aggregation must be indirect, these results imply that 4L/PS-NA mice are a good *in vivo* model to test new anti-aggregatory compounds against endogenous proteins.

Disclosures: E. Auer: None. **M. Farcher:** None. **R. Rabl:** None. **V. Schiffer:** None. **S. Flunkert:** None. **M. Posch:** None. **B. Hutter-Paier:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.29/V6

Topic: C.03. Parkinson's Disease

Support: NIH Grant T32GM008361

American Parkinson's Disease Association grant

Title: Spread of synuclein pathology following synuclein fibril injection in murine models

Authors: *L. STOYKA, H. ABDELMOTILIB, D. STANDAERT, L. VOLPICELLI-DALEY
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Abstract: Parkinson disease (PD) is the second most common neurodegenerative disease. Cardinal features include rigidity, resting tremor, bradykinesia, and postural instability. Although current treatments can temporarily improve motor symptoms, no current treatments stop disease progression. Insoluble inclusions known as Lewy bodies (LB) and Lewy neurites (LN), composed mostly of α-synuclein (α-syn), are diagnostic histopathological findings of PD. They are found throughout the nervous system includingthe substantia nigra pars compacta, cerebral cortex, and hippocampus; these aggregates correlate with onset and progression of PD and related synucleinopathies. We hypothesize preventing formation and spread of α-synpathology will prevent disease progression. Studying α-syn pathology is important for understanding the mechanisms of PD and can contribute to our understanding of disease progression. Injection of α-syn fibrils in animal models can induce robust inclusions that resemble the LB and LN found in diseased brains. Here, we describe the effect of injection location on inclusion formation at the site of injection and in interconnected brain regions. We evaluated injections in the striatum, cortex, and substantia nigra of C57BL/6J mice and found distinct patterns of inclusion formation. Striatal injections produced the most robust, consistent pathology with inclusions found in brain regions relevant for synucleinopathies. We will also present preliminary results on dysfunction in motor and cogntitive behavioral tests.

Disclosures: L. Stoyka: None. **H. Abdelmotilib:** None. **D. Standaert:** None. **L. Volpicelli-Daley:** None.

Poster

131. Alpha-Synuclein Aggregation and Transmission

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 131.30/V7

Topic: C.03. Parkinson's Disease

Support: NIH grant NS059869

Title: Apoptosis signal-regulating kinase 1 modulates the phenotype induced by α-Synuclein fibrils in mice

Authors: *J. ZHANG, E. PARK, H. PARK, R. YAN, E. JUNN, M. M. MOURADIAN
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Abstract: Alpha-Synuclein (α-syn) is a key pathogenic protein in α-synucleinopathies including Parkinson's disease (PD) and Dementia with Lewy Bodies. Accumulating evidence from studies of postmortem human brains, rodent models and cultured neurons show that misfolded preformed fibrils (PFF) of α-syn are transmitted from cell-to-cell, a phenomenon that correlates with clinical progression and emergence of additional neuropsychiatric manifestations as the disease advances. We previously showed that deleting the MAP3 kinase Apoptosis Signal-Regulating Kinase 1 (ASK1), which is a central player linking oxidative stress with neuroinflammation, mitigates the neuronal damage and neuroinflammation induced by transgenic α-synuclein over-expression in the mouse brain and improves the motor performance of the animals. However, whether ASK1 impacts α-syn PFF transmission and disease progression remains unclear. Here, we compared the neuropathological and behavioral phenotype of ASK1 knock-out mice with that of wild-type mice following intrastriatal injection of α-syn PFF. At six months post-injections, we found that lack of ASK1 is associated with reduced amount of phosphorylated α-synuclein aggregates in the striatum and cortex, as well as less profound loss of striatal dopaminergic nerve terminals and nigral tyrosine hydroxylase immunoreactivity. Additionally, the neuroinflammatory reaction to α-syn PFF injection and propagation seen in wild-type mice was markedly attenuated in ASK1 knock-out animals. These neuropathological markers of diminished toxicity of α-syn PFF in the absence of ASK1 was associated with better behavioral performance including on the rotarod, wire hang test and nesting behavior compared to wild-type mice. These data suggest that ASK1 plays an important role in pathological α-synuclein fibril transmission and neuroinflammation, and consequently may impact disease progression. These findings collectively raise the possibility that ASK1 provides a target for developing therapeutics designed to slow the progression of PD and related α-synucleinopathies.

Disclosures: J. Zhang: None. **E. Park:** None. **H. Park:** None. **R. Yan:** None. **E. Junn:** None. **M.M. Mouradian:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.01/V8

Topic: C.03. Parkinson’s Disease

Support: The Selma Schottenstein Harris Lab for Research in Parkinson's

The Gardner Family Center for Parkinson's Disease and Movement Disorders

Title: Neuronal degeneration in non-dopaminergic brain regions and neurochemical alterations in the DJ-1 knockout rat model of Parkinson’s disease

Authors: *T. L. KYSER[1], A. J. DOURSON[1], K. H. LUNDGREN[1], R. GULATI[1], A. GUTIERREZ[2], C. V. VORHEES[3], K. B. SEROOGY[1]
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Abstract: Loss of function mutations in the DJ-1 (PARK7) protein, first discovered in Dutch and Italian families, results in an autosomal recessive inherited form of Parkinson’s disease (PD). DJ-1 has numerous functions, including, for example, antioxidant properties, mitochondrial maintenance, mitophagy, autophagy, and microglial activation, all of which are implicated in PD. Hallmarks of PD are deficits in both motor and non-motor behaviors, as well as degeneration of areas such as the dopaminergic (DA) substantia nigra pars compacta (SNpc), noradrenergic (NE) locus coeruleus (LC), and serontonergic (5HT) dorsal raphe nucleus (DRN). Previous findings in the DJ-1 knockout (KO) mouse have indicated mild motor dysfunction, no cell loss in any region associated with PD, and little change in non-motor behaviors. In contrast, our previous work has shown that DJ-1 KO rats exhibit non-motor abnormalities, including short-term spatial memory deficits and despair. Here, we examined the DJ-1 KO rat vs wild-type (WT) controls for age-related neurodegeneration, via unbiased stereological cell counts of tyrosine hydroxylase (TH)+ cells in the SNpc, and LC and of tryptophan hydroxylase (TPH)+ neurons in the DRN. We also analyzed changes in in monoamine levels in various brain regions at 5 and 9 months of age, using HPLC. In the DRN, we observed greater numbers of TPH+ cells at 5 months of age in the DJ-1 KO vs WT animals. We also found an overall loss of TPH+ cells between 5 months and 17 months of age in the DJ-1 KO rats but not in the WT rats. In the LC, we found a loss of TH+ neurons at 17 months of age between the DJ-1 KO and WT animals. And again, we detected an overall loss of TH+ cells between 5 and 17 months of age in only the DJ-1 rats. In the SNpc, there was no significant change in the number of TH+ cells at any time point when comparing the WT and DJ-1 KO animals. However, we did observe an overall loss of TH+ neurons in both groups between 5 and 17 months of age. Our preliminary cell counts of

Iba-1+ microglia in the SNpc and striatum at 17 months of age revealed no differences between DJ-1 KO rats and WT controls. Our neurochemical analyses indicate changes in DA and its metabolites, and the 5HT metabolite 5-HIAA, in the striatum at 9 months of age. Moreover, we found a decrease in NE and an increase in 5-HIAA in the hippocampus at 5 months of age. Ongoing studies will determine monoaminergic changes in additional brain regions. Taken together, these results indicate age-related neurodegeneration in brainstem regions associated with depression and other psychiatric disorders. These findings may indicate that the DJ-1 KO rat is a good model for the prodromal stage of PD, which is characterized by non-motor symptoms.

Disclosures: T.L. Kyser: None. **A.J. Dourson:** None. **K.H. Lundgren:** None. **R. Gulati:** None. **A. Gutierrez:** None. **C.V. Vorhees:** None. **K.B. Seroogy:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.02/V9

Topic: C.03. Parkinson’s Disease

Support: Adrienne Helis Malvin Medical Research Foundation

Title: Protein translation factor eIF4G1 mutation exhibit alter protein synthesis and selective neurodegeneration of dopamine neurons

Authors: *S. S. KARUPPAGOUNDER[1,2,7], H. JIA[1,3,7], Y. LEE[1,2,4,8,9], S. M. EACKER[1,2], J. KIM[2,3,7], E. NORDQUIST[2,10,11], N. LONGSON[2,10], Z. ROCCAFORTE[2,10], S. BRAHMACHARI[1,2,7], M. KUMAR[1,2], X. MAO[1,2], S. A. ANDRABI[1,2,12], D. SWING[13], L. TESSAROLLO[13], H. JIANG[1,2,7], I. MARTIN[1,2,14], T. M. DAWSON[2,1,5,6,7], V. DAWSON[2,1,3,6,7]
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Abstract: Eukaryotic translation initiation factor gamma 1 (EIF4G1) is involved in protein translation serving as a scaffold component in a mRNA translation initiation complex that performs a key role in both cap-dependent and cap independent translation initiation. Parkinson's disease (PD) is the second most common neurodegenerative disorder. Recent studies identified point mutations in the EIF4G1 gene in autosomal dominant PD, potentially linking EIF4G1 and protein translation with PD. Recent findings from our laboratory show that the alterations in protein translation contributes to LRRK2 mediated neurodegenerations. However, sequencing studies indicated mutations of EIF4G1 seemed to be rare, and standard genetic approaches have not been able to confirm whether monogenetic EIF4G1 mutations are sufficient to cause PD. To explore the pathological role of EIF4G1 in *in vivo studies*, we generated conditional EIF4G1 transgenic mice expressing wild type and disease associated mutants (R1205H or A502V) EIF4G1 and *Drosophila* models expressing human EIF4G1 in dopaminergic neurons. Using i*n vitro* studies, to understand if and how the mutations alter the function of eIF4G1, we generated EIF4G1 mutation knock-in cells, using CRISPR/Cas9 technology. Mice express that express high levels of eIF4G1 disease associated mutant eIF4G1 develop progressive degeneration of dopaminergic neurons in the SNpc, and exhibit behavioral deficits that are not observed in transgenic wild type eIF4G1 or littermate control mice. In the *drosophila* model, we found that RH-EIF4G1 and AV-eIF4G1 transgenic flies exhibit early mortality, late-onset locomotion impairment, and age-related dopaminergic neurodegeneration. In EIF4G1 mutation cell lines, we found repression of global protein translation and altered cap-dependent and cap-independent translation. These data suggest that these mutations in EIF4G1 play a role in the pathogenesis of PD, suggesting that downregulation of mRNA translation may play a role in neurodegeneration. Further studies are required to identifying the specific mRNAs affected by eIF4G1 mutations, which will lead better understanding of PD and potential novel therapeutic targets for PD.

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Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.03/V10

Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation

Title: A novel model of alphavirus induced Parkinsonism in outbred CD-1 mice

Authors: *C. BANTLE
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Abstract: Parkinson's Disease (PD) is characterized by loss of voluntary motor control, degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNpc), α-synuclein aggregation and gliosis. Lack of appropriate animal models has limited our understanding of PD pathogenesis and hindered the development of better therapeutic interventions. Current animal models based on the use of neurotoxins and transgenic mice may show loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) but often lack other key hallmarks of the disease, such as protein aggregation and assymetry. Notably, certain neurotropic mosquito-borne alphaviruses, such as Western equine encephalitis virus (WEEV), can target the SNpc with high fidelity and have been known for many years to cause neurological symptoms resembling PD in individuals who develop encephalitic disease. Using recombinant WEEV expressing firefly luciferase in outbred CD-1 mice, we demonstrate that infection by simple intranasal inoculation results in rapid distribution throughout the cortex and basal ganglia, pronounced neurobehavioral abnormalities, marked glial activation and loss of dopaminergic neurons in the SNpc. To prevent mortality, mice were treated with polyclonal antibodies to the WEEV E1 viroporin at 12 and 48 hours post-infection, whereupon they cleared WEEV and remained viable for at least two months. Levels of viral replication were monitored by *in situ* bioluminescence imaging for the entire eight weeks of infection. Brain tissue was fixed and cryosectioned for 3D design-based stereology. CLARITY imaging revealed wide distribution of RFP-expressing WEEV throughout the CNS. Intranasal inoculation with recombinant WEEV showed high specify for the SNpc and caused significant DA cell loss, along with glial cell activation and a gene expression profile consistent with PD-like pathology. This study provides a new viral- based PD animal model that closely replicates the neuroenigmatic and insidiousanatomical features of pathogenesis of PD. This viral system can be appliedis readily applicable to existing genetic transgenenic based PD models of PD and more closely related human models for therapeutic and mechanistic research.

Disclosures: C. Bantle: None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.04/V11

Topic: C.03. Parkinson's Disease

Title: Retinal biomarkers in a seeded mouse model of Parkinson's Disease: Pathological α-synuclein induces accumulation of phosphorylated α-synuclein (p129S) and tau (pThr231), inflammation, metabolic dysregulation and cell death

Authors: *N. MAMMADOVA[1], C. M. SUMMERS[2], R. D. KOKEMULLER[3,5], T. BARON[6], R. J. VALENTINE[2], D. S. SAKAGUCHI[1], A. G. KANTHASAMY[4], J. J. GREENLEE[5], M. H. W. GREENLEE[3]
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by accumulation of misfolded α-synuclein within the central nervous system (CNS). Although non-motor clinical phenotypes of PD such as visual dysfunction have become increasingly apparent, retinal pathology associated with PD is not well understood. In this study, we show the progression of retinal pathology in a transgenic mouse model (TgM83) expressing the human A53T mutated α-synuclein. Additionally, TgM83 mice were intracerebrally (IC) inoculated with brain homogenate from TgM83 mice with clinical signs of motor system disease. The purpose of this study was to investigate the effect of α-synuclein "seeding" or propagation throughout the CNS, on retinal pathology. We analyzed retinas of homozygous TgM83 mice at 5, 8, and 12-18 (clinical illness) months of age. Our controls included age-matched B6C3H mice (genetic background of the TgM83 mouse model). We assessed retinal tissues using western blotting, and immunohistochemistry for α-synuclein (pSer129), tau (pThr231), tyrosine hydroxylase (specific to dopaminergic amacrine cells in the retina), glial fibrillary acidic protein (GFAP), microglia specific proteins (Iba1 and CD68), autophagy specific markers (LC3a/b, and Beclin-1), and apoptosis associated markers (PKC-δ, and caspase-3). Our results show specific phenotypic changes associated with the A53T mutation. Retinas of non-inoculated TgM83 mice had accumulation of α-synuclein (pSer129) and "pre-tangle" tau, progressive activation of retinal glial cells, and photoreceptor cell loss appreciable after 8 months of age. Inoculation with brain homogenate from clinically affected TgM83 mice, resulted in accelerated development of pathological biomarkers. Compared to non-inoculated - TgM83 mice, we show increased accumulation of α-synuclein (pSer129) and tau (pThr231) proteins (~7-fold increase), increased CD11b, and CD68 immunoreactivity (~2.5 fold; ~3-fold increase respectively), signs of autophagic dysregulation, as well as evidence of neuronal loss in retinas of inoculated mice at 5 months of age. Our work suggests that inoculation, or seeding with brain homogenate from clinically ill TgM83 mice accelerates retinal pathology. Misfolded α-synuclein may induce accumulation of α-synuclein (pSer129), tau (pThr231) in retinal neurons and glia, leading to acceleration of inflammation, metabolic dysregulation, and photoreceptor cell death. Our work provides novel insight into retinal phenotypes associated with Parkinson's disease, and may contribute to a better understanding of visual symptoms experienced by patients.

Disclosures: **N. Mammadova:** A. Employment/Salary (full or part-time):; Iowa State University. **C.M. Summers:** None. **R.D. Kokemuller:** None. **T. Baron:** None. **R.J. Valentine:** None. **D.S. Sakaguchi:** None. **A.G. Kanthasamy:** None. **J.J. Greenlee:** None. **M.H.W. Greenlee:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.05/V12

Topic: C.03. Parkinson’s Disease

Title: Following the neuropathology of Parkinson’s disease with magnetic resonance imaging: Alterations in resting state functional connectivity and gray matter microarchitecture in PINK1 -/- rats

Authors: *X. CAI[1], T. MORRISON[1], J. QIAO[2], S. MALMBERG[1], J. SABRICK[1], S. IRIAH[1], J. C. HARTNER[4], M. TRIVEDI[5], P. KULKARNI[1], C. F. FERRIS[1,3]
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Abstract: The combination of genetic models of Parkinson’s disease (PD) coupled with advanced imaging techniques can elucidate neurobiological and behavioral aspects of disease progression and have been increasingly useful for identifying early biomarkers of PD. PTEN-induced putative kinase 1 (PINK1) is a mitochondrial protein kinase involved in protecting neurons from stress-induced mitochondrial dysfunction. Mutation in the PINK1 gene is a leading risk factor in autosomal recessive familial PD and accordingly, PINK1 knock-out (KO) rat models show motor dysfunction that are analogous to human PD patient symptomology. In this study, we combined various MR imaging modalities e.g., resting state functional connectivity MRI (rs-fcMRI), diffusion weighted imaging (DWI) and quantitative ultra-short time-to-echo, contrast enhanced imaging (QUTE-CE) to identify neurobiological differences between WT and PINK1 -/- rats. These studies were conducted between 6-8 months of age. All voxel based measures for each modality were registered to a rat MRI atlas with 172 segmented, annotated brain regions. DWI and quantitative anisotropy was used to follow neuroadaptation or changes in gray matter microarchitecture in the basal ganglia, mesencephalic dopaminergic system, limbic cortex and hippocampal complex. Resting state fcMRI showed altered resting state connectivity between basal ganglia, septum and somatosensory cortex, while QUTE-CE showed changes in capillary density across several brain areas involved in pain processing between vehicle controls and OXY treated animals.

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Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson’s Disease

Support: NIH NINDS Grant R01NS082565

Priority Target Grant 11380 from The Michael J. Fox Foundation for Parkinson's Research

Title: Behavioral, histological and electrophysiological analysis of PINK1 knockout rats

Authors: L. J. MCMEEKIN[1], E. E. UBOGU[1], G. C. ROWE[2], Y. TANG[2], A. M. SCHONHOFF[1], A. F. MANUEL[1], A. LONG[1], N. BRYANT[1], N. K. MOKHA[1], A. M. RIZWAN[1], M. V. KING[1], R. B. CREED[1], S. M. WILSON[2], *M. S. GOLDBERG[1]
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Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease. The primary clinical symptoms include bradykinesia, rigidity, postural instability and tremor. PD is characterized pathologically by the loss of dopaminergic neurons in the substantia nigra and the presence of alpha-synuclein immunoreactive intracellular inclusions termed Lewy bodies. Loss-of-function mutations in PTEN-Induced kinase 1 (PINK1) are causally linked to an inherited form of PD with onset of symptoms at atypically early age. PINK1 knockout (KO) rats model key features of PD including age-dependent locomotor behavior deficits, loss of nigral dopamine producing neurons and synuclein immunoreactive pathology. We conducted behavioral, histological and electrophysiological analyses of PINK1 knockout rats at various ages in order to determine the underlying cause of the most prominent behavioral phenotype, which is hind limb partial paralysis (paraparesis). Wild-type (WT) and PINK1 KO rats were analyzed using multiple behavioral tests sensitive to locomotor dysfunction, including open field, gait analysis, footslip analysis and dynamic weight bearing. The results confirm robust locomotor deficits that begin between 6 and 7 months of age, but then subside instead of progressing. Spinal cord sections of WT and PINK1 KO rats were examined by immunohistochemistry with antibodies to markers of neuroinflammation, including Iba1 and CD68, and with antibodies specific for synuclein, ubiquitin, and other markers of neuropathology. Unbiased stereology was used to estimate the number of lower motor neurons in the thoracic and lumbar spinal cord. We found no evidence of loss of lower motor neurons in PINK1 KO rats, indicating that the paraparesis phenotype is not due to lower motor neuron loss. This contrasts with the motor symptoms of amyotrophic lateral sclerosis (ALS) and the locomotor phenotypes of ALS animal models, which are primarily due to lower motor neuron loss. Confocal microscopy was used to measure the integrity of neuromuscular junctions labeled

with Alexa-555 conjugated alpha-bungarotoxin. Electrophysiological analysis of sciatic nerves in live rats revealed a ~50% decrease in compound motor action potential (cMAP) amplitude in age 6-7 month PINK1 KO rats, but normal cMAP amplitude at pre- and post-symptomatic ages. Nerve conduction velocity was normal at all ages indicating no demyelination. Our data is consistent with axon terminal dysfunction causing the hind limb paresis phenotype in PINK1 KO rats. We speculate that synaptogenesis and sprouting of new axon terminals contribute to recovery of motor function in PINK1 KO rats.

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Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson’s Disease

Support: Argentina MINCYT-PICT 2013-1109

ISN-CAEN

CONICET (Argentina) fellowship to AD

Title: Tau isoforms imbalance related to motor deficits in a mouse model of tauopathy

Authors: A. DAMIANICH[1], M. SARTOR[1], S. L. ESPINDOLA[2], *J. E. FERRARIO[3,4], M. AVALE[1]
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Abstract: The microtubule associated protein Tau is highly expressed in neurons and involved in microtubule dynamics and axonal transport. Tauopathies are neurodegenerative diseases related to abnormal tau metabolism, including the abnormal content of certain Tau isoforms. Particularly, the alternative splicing of exon 10 (E10) in tau primary transcript produces isoforms of 3 and 4 microtubule binding repeats (3R and 4R). The normal adult brain expresses equal amounts of 3R and 4R isoforms, while imbalances in their relative content are associated with tau pathology. Tauopathies such as Progressive Supranuclear Palsy (PSP) and frontotemporal dementia that affect the basal ganglia, lead to parkinsonism. In many cases a 3R/4R imbalance is present. Here we investigated motor phenotypes and neurochemical changes in the striatum and *substantia nigra pars compacta* (SNpc) of hTAU mice, a model of tauopathy with abnormal

content of tau isoforms. We compared WT *versus* hTAU mice in open field spontaneous locomotion, motor coordination tasks and cognitive performance. Dopamine (DA) and its metabolites were quantified by HPLC. The relative amount of tau isoforms and levels of hyperphosphorylated tau were determined by western blot. Our analyses show that hTAU mice are severely impaired in motor coordination, however striatal DA levels are equivalent to WT mice. Moreover, no hyperphosphorylated tau deposits were detected in the striatum nor in the SNpc of hTAU mice. Howeve, hTAU mice display an excess of 3R tau isoform in the striatum, while WT mice only contain 4R Tau. We hypothesized that striatal tau isoforms imbalance could underlie the observed motor phenotypes. Thus, we used a *trans*-splicing RNA reprogramming strategy to control the inclusion of E10 in the endogenous tau transcript with lentiviral vectors, delivered into the striatum of hTau mice. Our study suggests that motor phenotypes observed in the hTAU model are related to an imbalance in tau isoforms in the striatum, therefore, we propose hTAU mice as a suitable model to study molecular mechanisms underlying the pathological role of Tau in the basal ganglia and postulate that modulation E10 inclusion by *trans*-splicing could be a potential therapeutical approach.

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Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson’s Disease

Support: NINDS Grant T32-NS082168

Title: Partial loss of ATP13A2 causes gliosis independent of robust lipofuscinosis

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Abstract: Homozygous or compound heterozygous *ATP13A2* mutations are associated with three clinically overlapping neurodegenerative diseases: a form of Parkinson’s disease termed Kufor-Rakeb syndrome (KRS), a lysosomal storage disorder termed neuronal ceroid lipofuscinosis (NCL), and a form of hereditary spastic paraplegia (HSP). Furthermore, recent data suggests that heterozygous carriers of mutations in *ATP13A2* may confer risk for the development of Parkinson’s disease, mimicking the association of mutations in glucocerebrosidase with both Parkinson’s disease and a lysosomal storage disorder. Mutations in

ATP13A2 are generally thought to be loss of function; however, the lack of autopsy tissue has prevented the field from determining the pathological consequences of losing functional ATP13A2 in humans. We and others have previously characterized mice completely lacking murine Atp13a2, demonstrating the presence of lipofuscinosis within the hippocampus - a key feature of NCL. We have now extended the pathological characterization of homozygous *Atp13a2* knockout mice to define the regional distribution of lipofuscinosis in the brains and determine whether other tissues are affected by the loss of Atp13a2. Futhermore, to determine if loss of one functional Atp13a2 allele can serve as a risk factor for disease, we have now assessed heterozygous *Atp13a2* mice for key features of NCL. Pathological studies indicate that lipofuscinosis, a key feature of NCL, and elevated gliosis are prevalent in the cortex, hippocampus, cerebellum, and brainstem of homozygous *Atp13a2* homozygous knockout mice compared to wildtype controls. Loss of one functional Atp13a2 allele leads to both microgliosis and astrocytosis in multiple brain regions compared to wildtype controls; however, elevated levels of lipofuscin were only modestly high in the cortex of heterozygous *Atp13a2* knockout mice. These data strongly support that complete loss of ATP13A2 is most likely causative for the lysosomal storage disease, NCL, rather than a form of Parkinson's disease, KRS, in humans. Additionally, these data suggests the possibility that partial loss of ATP13A2 causes inflammatory changes within the brain which appear to be independent of robust lipofuscinosis. This elevated gliosis independent of robust lipofuscinosis indicates that the brain may be under constant stress attempting to compensate for the partial loss Atp13a2 and possibly making the cells vulnerable to secondary insults which could elicit further pathology and potentially play a role in disease presentation.

Disclosures: S. Rayaprolu: None. **Y. Seven:** None. **J. Howard:** None. **C. Duffy:** None. **L. Rousseau:** None. **M. Castanedes:** None. **E. Rodriguez:** None. **P. Schultheis:** None. **G. Mitchell:** None. **J. Lewis:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 132.09/V16

Topic: C.03. Parkinson's Disease

Title: *In vivo* PET quantification of CRISPr/Cas9 conditional gene knockdown in rats

Authors: *S. MARCIANO, K. HERFERT, L. KUEBLER, A. MAURER, B. J. PICHLER department of preclinical imaging and radiopharmacy, Werner Siemens Imaging Ctr., Tübingen, Germany

Abstract: Neurotoxic effects of misplaced dopamine (DA), related to its cytosolic accumulation and oxidative products formation, play a role in the Substantia Nigra (SN) degeneration in

Parkinson´s disease (PD). Hence, DA packaging by the vesicular monoamine transporter 2 (VMAT2) seems to be crucial to attenuate the demise of nigrostriatal neurons. Indeed VMAT2 expression inversely relates with PD. To provide insights into PD pathogenesis, we performed a CRISPr/Cas9 conditional knockdown (KD) of the VMAT2 gene (slc18a2) in rats expressing the Cre-recombinase under the DA transporter (DAT) promoter. Following the selective KD, VMAT2 expression, DA nerve terminals density and DA availability changes were quantified by PET with ^{11}C-DTBZ, ^{11}C-methylphenidate and ^{11}C-raclopride.

To induce a conditional KD in nigrostriatal DA neurons, two double-floxed adeno-associated viral (AAV) vectors expressing SaCas9 and the guide RNA (sgRNA) scaffolds were used. We designed five sgRNAs for slc18a2 and one for the Lac*Z,* as control, and tested their KD efficiency in primary cortical neurons and N27 cells using a third AAV-Cre. The KD efficiency of the sgRNAs was assessed on DNA (surveyor) and protein (immunofluorescence) level. Following the *in vitro* selection, the best guide was purified and injected with the AAV-SaCas9 (1:1 ratio) ($6x10^{14}$ gc/mL) into the SN of DAT-Cre rats (slc18a2 KD: n=3; LacZ: n=2). DPBS was injected on the contralateral side. Dynamic PET scans were performed 4w, 12w post-injection. Volumes of interest were placed over the striatum and cerebellum of the anatomical MRI to generate time activity curves. Logan Reference kinetic modeling was applied to calculate the binding potential (BP_{ND}).

The *in vitro* data show, despite the low efficiency due to the three AAVs transduction, that two of the five sgRNAs were able to induce a KD of the target gene and protein, if SaCas9, sgRNA and Cre were successfully co-expressed. After injection of the best sgRNA in DAT-Cre rats, we found a significant 3% decrease of VMAT2 expression at 4w ($p=0.001$) and a trend towards a 6% at 12w ($p=0.07$), while there was no change in the control rats. MP and RAC BP_{ND} showed no differences within the groups at 4w and 12w.

To improve the *in vitro* efficiency, FACS sorting of the transduced neurons will be performed. Our preliminary *in vivo* data indicate that we were able to selectively KD the VMAT2 gene using the CRISPr/SaCas9 system without affecting dopaminergic nerve terminals and postsynaptic receptor availability in DAT-Cre rats. *Ex vivo* analysis is ongoing to validate the AAVs expression and KD efficiency. In future experiments, we aim to inject more rats with a higher viral volume to increase the KD efficacy.

Disclosures: S. Marciano: None. **K. Herfert:** None. **L. Kuebler:** None. **A. Maurer:** None. **B.J. Pichler:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson’s Disease

Support: Delaware Economic Development Office Pilot Grant

NIH/NIA K01 Grant Support to HL

Title: Pesticides interactions in a *Drosophila* model of parkinson's disease

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Abstract: The etiology of Parkinson's disease (PD) the second most common neurodegenerative disease affecting 1% of the population aged 65 and above remains elusive. Epidemiological and animal model studies have identified pesticides as risk factors for the disease. However, the combinations of pesticides that elevate PD susceptibility have not been fully elucidated. Moreover, a number of these studies depend on chemicals that are either of limited use (e.g., rotenone) or have been banned from use in the U.S and the EU (e.g., paraquat). Our research goal is to develop multiple-hit toxin animal models that reflect the synergistic toxicities from commonly-used pesticides. We used the *Drosophila* model to test the link between exposure to pesticide combinations and PD risk. We investigated whether different concentrations of commonly-used pesticides such as acephate, alachlor and atrazine could cause additive or synergistic damage relevant to PD. We exposed *Drosophila* to commercially-used pesticides at a range of concentrations and measured both their survival and different aspects of their locomotive activity. We report that two-pesticide combinations involving acephate and alachlor had a synergistic effect on locomotion and organismal survival in flies. Further, we present a report of our analysis of the effect of these pesticide combinations on DA neuron survival. Together, these findings bring new insights into the level of risk that may be associated with commercially-used pesticides using the *Drosophila* model.

Disclosures: K. Patel: None. **M. Heredia:** None. **Y. Martinez:** None. **H.O. Lawal:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson's Disease

Support: FAPESP

Capes (Brazil)

CNPq

Title: The possible involvement of the TRPM7 channel and of miR-22 in a model of Parkinson's disease in mice

Authors: P. C. G. GARCIA[1], C. C. REAL[2], *L. R. BRITTO[1]
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Abstract: Parkinson´s disease (PD) is a progressive neurodegenerative disease characterized by the reduction of dopaminergic neurons in the substantia nigra pars compacta, resulting in DA decrease in striatum. Recently, transient receptor channels (TRP) have been studied in neurodegenerative diseases development. The function of one of these channels, TRPM7, has been related to ischemia, hypoxia and epilepsy. This study aims to analyze the involvement of those channels in PD, and the involvement of miR-22 (microRNA that targets TRPM7) in this disease. For this study, we used 2 months old mice (C56Bl/6J) and induced to PD by 6-OHDA unilaterally. 7 days after injury the animals were decapitated and the midbrain and striatum were collected to analyze the expression of tyrosine hydroxylase (TH - for evaluation of neuronal death), TRPM7 by immunoblotting and miR-22 by RT-PCR. At day 7 after 6-OHDA injection, our data showed TH reduction in striatum (60%, $p \leq 0.05$), and in midbrain (40%, $p \leq 0.05$) compared to the control hemisphere. In addition, our results showed an increase of 117% in TRPM7 expression in the experimental midbrain compared to the control hemisphere ($p \leq 0.05$), whereas there was a reduction of 63% in the expression of miR-22 in the experimental hemisphere compared to the control hemisphere ($p \leq 0.01$). In the striatum, there was no difference in the expression of TRPM7 and miR-22 when compared to the experimental hemisphere and control hemisphere with these techniques.
Thus, the present study suggests that TRPM7 is involved in neurodegeneration in the 6-hydroxydopamine model of Parkinson´s disease and concomitant with this, the exposure of dopaminergic cells to 6-OHDA can modulate miR-22, which may be helpful in understanding of the pathophysiology of PD and to provide new knowledge for possible therapeutic interventions.
Financial support: FAPESP, CNPq, Capes (Brazil)
Key-words: Parkinson’s disease, 6-OHDA, TRPM7, miRNA, miR-22

Disclosures: P.C.G. Garcia: None. **C.C. Real:** None. **L.R. Britto:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

Location: Halls A-C

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Program#/Poster#: 132.12/V19

Topic: C.03. Parkinson’s Disease

Title: LRRK2 mutations impair autophagic clearance of aggregate-prone proteins by suppressing dynein

Authors: *Y. BANG[1], H. CHOI[2]
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Abstract: Accumulation of intraneuronal protein aggregates and defective microtubule and autophagy are commonly detected in the brain of neurodegenerative disease patients, such include leucine-rich repeat kinase 2 (LRRK2) mutations. However the exact mechanism in this process remains poorly defined. We have recently shown that LRRK2 disrupts aggresome formation which is a crucial step for aggregates removal, especially in the condition of aggregates accumulation induced by proteasome inhibitor, MG132. We reveal that LRRK2 G2019S mutation interferes with cAMP response element-mediated dynein expression, which is required for cytoskeleton rearrangement and perinuclear transport of protein aggregates to form aggresome. Cytoskeleton regulation using Latrunculin A up-regulates dynein expression and organizes microtubule into focused arrays, and ameliorates autophagy dysfunction and proteinopathy-related cytotoxicity in neuronal cells with G2019S. Our present findings provide an attractive clue for the precise mechanism underlying autophagy dysregulation in the brain of PD patients with LRRK2 mutation.

Disclosures: Y. Bang: None. **H. choi:** None.

Poster

132. Parkinson's Disease: Models, Mechanisms, and Targets

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Topic: C.03. Parkinson’s Disease

Support: CNPq

CAPES

FAPESC

FINEP

UFSC

Title: The role of the noradrenergic system and the effects of β-blockers in L-DOPA-induced dyskinesia in an animal model of Parkinson’s disease

Authors: *S. C. LOPES[1], P. A. DE OLIVEIRA[1], M. W. LOPES[2], B. LEAL[2], R. N. TAKAHASHI[1], R. D. S. PREDIGER[1]
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Abstract: Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies. The replacement of dopamine with the oral administration of the precursor L-DOPA is the main pharmacological alternative to the palliative treatment of motor symptoms (bradykinesia, resting tremors and muscular rigidity) of PD. However, about 90% of PD patients treated for 10 years with L-DOPA develop motor side effects, which include dyskinesia and on-off fluctuations. The exact molecular mechanisms involved in development of L-DOPA-induced dyskinesias (LIDs) remain unknown; however, some studies indicate the involvement of the noradrenergic system and the potential for β-adrenergic receptor antagonists as antidyskinetic agents. In this study it was investigated the role of selective or combined noradrenergic and dopaminergic degeneration, and the modulation carried out by β-adrenergic antagonists in the appearance and development of LIDs in rats infused unilaterally with the catecholaminergic neurotoxin 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle. Evaluation of abnormal involuntary movements (AIMs) during chronic treatment with L-DOPA demonstrated that the combined noradrenergic plus dopaminergic degeneration caused early appearance and increased severity of LIDs. While lesions induced by 6-OHDA following the pretreatment with desipramine or nomifensine, mostly dopaminergic or noradrenergic lesions, respectively; had lower scores of LIDs, as well as abnormal movements of locomotion. The L-DOPA efficacy in alleviate motor dysfunction was evaluated by the cylinder, open field and rota-rod tests; neither amantadine nor propranolol disrupted the antiparkinsonian activity of L-DOPA. Taken together, these results suggest that the noradrenergic system modulates LIDs and provide new evidence of the antidyskinetic potential of β-blockers agents in PD.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.01/V21

Topic: C.03. Parkinson’s Disease

Title: Increased serotonin transporter-mediated dopamine uptake in the dyskinetic striatum of L-DOPA-treated, hemi-parkinsonian rats

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Abstract: Parkinson’s disease (PD) is typically characterized by akinetic motor symptoms resulting from nigrostriatal dopamine (DA) loss. DA replacement therapy with the precursor L-DOPA is the gold-standard symptomatic treatment; however, chronic administration usually

leads to debilitating abnormal involuntary movements (AIMs) referred to as L-DOPA-induced dyskinesia (LID). Over the last several years, the serotonin (5-HT) system has been shown to play an essential role in LID development and expression. One target, the 5-HT transporter (SERT), has gained recent interest as pharmacological SERT blockade conveys pronounced anti-dyskinetic effects. New evidence from our lab suggests that 6-hydroxydopamine (6-OHDA) and L-DOPA induce a functional shift in DA uptake from the DA transporter (DAT) to the SERT; however, the nature of this shift is unclear. Therefore, the current experiments sought to determine how DA lesions and L-DOPA treatment (6 mg/kg + benserazide 15 mg/kg; s.c.) in adult male Sprague-Dawley rats affected SERT mRNA expression in the dorsal raphe nucleus, synaptosomal protein expression in the striatum, and SERT function through striatal DA uptake using *ex vivo* microdialysis. Three weeks following unilateral sham or 6-OHDA lesion surgery, DA-lesioned rats were sorted into equivalently motor impaired treatment groups and primed for 2 weeks with either daily vehicle or L-DOPA. AIMs and rotations were monitored at the end of priming to confirm equally dyskinetic treatment groups. DAT mRNA was significantly reduced in the substantia nigra due to 6-OHDA while SERT mRNA remained stable. Similar effects were seen in synaptosomal DAT and SERT protein in the striatum, however a significant interaction between DA lesion and L-DOPA treatment revealed an increase in SERT:DAT ratios which positively correlated with LID expression. Finally, using the DAT and SERT blockers GBR12909 and citalopram, respectively, on synaptosomal striatal tissue from DA-lesioned rats primed with either vehicle or L-DOPA, we determined 6-OHDA- and L-DOPA-induced changes in DAT and SERT function of extracellular DA uptake. We found that DA lesion and L-DOPA reduced DA uptake via DAT and that, together, 6-OHDA-induced DA loss and L-DOPA treatment significantly increased DA uptake via SERT. Overall, 6-OHDA-induced DA loss and L-DOPA treatment does not affect SERT mRNA or striatal protein expression; however, in the dyskinetic striatum, SERT appears to be primarily responsible for extracellular DA uptake implicating SERT's burgeoning role in DA signaling during LID development and expression.

Disclosures: **M. Conti:** None. **D.F. Werner:** None. **C.R. Bishop:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

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Title: Co-treatment of the C-terminal domain fragment of tetanus toxin and pramipexole improves motor behavior and ameliorate oxidative stress against a dopaminergic lesion with 6-hydroxydopamine in rats

Authors: *F. PATRICIO MARTÍNEZ[1], F. PEREZ[5], S. MONTES[5], I. MARTINEZ GARCIA[2], F. LUNA[3], J. AGUILERA[6], L. MARTINEZ MENDIETA[4], I. D. LIMON[4]
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Abstract: The trophic activity of some drugs has given guidelines to propose new therapeutic strategies for Parkinson's disease (PD). Recently studies have shown that the C-terminal domain fragment of tetanus toxin (Hc-TeTx) has neuroprotective activity in animal models of PD. Also, pramipexole (PPX), currently used in the therapeutic of PD, has neuroprotective and antioxidant activity due to agonism with dopaminergic receptors D_2/D_3. The objective of this study was to evaluate motor behavior, levels of lipid peroxidation (LPX), reactive oxygen species (ROS) and superoxide dismutase (SOD) activity in striatum of hemiparkinsonian rats. Male Wistar rats were used approximately 280-350 g; they were intracranially administered with 6-OHDA [16 μg/2μL] into the dorso-lateral striatum by stereotactic surgery. The next day, one group of animals received the Hc-TeTx fragment (20 μg/kg i.m. every 24 hours) for three days plus chronic administration of PPX (1 mg/kg v.o. every 12 hours) for 30 days. The following groups were created: intact, vehicle, 6-OHDA/vehicle/vehicle, 6-OHDA/Hc-TeTx/vehicle, 6-OHDA/PPX/vehicle, 6-OHDA/Hc-TeTx/PPX. Motor behavior was evaluated four days pre-injury and at 20 and 30 days post-lesion with 6-OHDA. At 30 days post-treatment the brains were obtained and the striated nucleus was extracted for the determination of lipid peroxidation, as well as the determination of the levels of reactive oxygen species (ROS). The results show a decrease in the percentage of use of both forelimbs in the cylinder model and a decrease in latency and number of steps to cross the beam walking model, in the 6-OHDA group with respect to the control group. The animals treated with 6-OHDA/Hc-TeTx/PPX improved the motor behavior respect with 6-OHDA group. Furthermore, the treatment with Hc-TeTx or PPX plus 6-OHDA had similar effects on the motor behavior. In contrast, the levels of ROS and LPX from striatum were found lower in the group 6-OHDA/Hc-TeTx/PPX respect to the other treatments. In the levels of SOD activity there are not changes between experimental groups. In conclusion, our results suggest that Hc-TeTx/PPX treatment improves motor behavior by its antioxidant action in hemiparkinsonian rats.

Disclosures: **F. Patricio Martínez:** None. **F. Perez:** None. **S. Montes:** None. **I. Martinez Garcia:** None. **F. Luna:** None. **J. Aguilera:** None. **L. Martinez Mendieta:** None. **I.D. Limon:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.03/V23

Topic: C.03. Parkinson’s Disease

Title: Behavioral assessment of Ldopa induced dyskinesia in rat: A new scoring scale

Authors: *S. LOIODICE[1], A.-S. DENIBAUD[1], W. DEFFAINS[1], M. ALIX[1], P. MONTAGNE[1], M. SEFFALS[2], C. DRIEU LA ROCHELLE[1]
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Abstract: Drug-induced dyskinesia is a frequent debilitating complication in Parkinson’s disease (PD) associated with physical and social disabilities. For decades, substantial research efforts have been invested into novel therapeutics able to alleviate the quality of life of patients. Of crucial importance is the development of a validated, standard and robust rating scale allowing to clearly quantify during preclinical studies the severity of these abnormal involuntary movements (AIMs) in a drug discovery perspective. The 6-hydroxidopamine (6-OHDA) dyskinesia model developed in the rat by Cenci et al, 1998 is recommended for testing compounds. Although extremely valuable, this rating scale relies on measurement of the frequency but not the intensity of abnormal involuntary movements. This limitation was later counterbalanced by other studies which added an amplitude score. However, a lack of reproducibility between these scales has been pointed out, illustrating the need to standardize the method. We sought to propose an adapted method aiming at refining the assessment of L-dopa-induced dyskinesia (LID) in the rat 6OHDA dyskinesia model.
A unilateral stereotaxic injection of 6-OHDA into the medal forebrain bundle was performed in rats. Animals with a severe lesion (>80% of cell loss) were selected using the apomorphine-induced rotation test. Severely lesioned rats were daily administered with L-dopa (20 mg/kg) and benserazide (5 mg/kg) over a 3-week period starting from week 4 post-lesion. Then, a single dose of amantadine (20, 30 or 40 mg/kg) was coadministered with L-dopa/benserazide. Animals were videotracked during 90 minutes after each L-dopa administration (priming and amantadine treatment). An adapted rating scale was used to score the LID. Briefly, AIMs were classified into different subtypes. Each rats were observed during 1 minutes every 20 minutes and a frequency score between 0 and 3 (0=absent, 1=occasional, 2=intermittent, 3=often) was attributed for each AIMs subtype. Then, a severity coefficient was applied depending on the feature of the observed AIMs.
A gradual time-dependent increase (by 3 fold) of the LID score was observed over the 3 week-period of Ldopa treatment. Furthermore, the rating scale was sensitive enough to highlight the amantadine-mediated decrease (by 2.2 fold) of the LID score in a dose-dependent manner.

Our study provides evidences highlighting the value of a new method for the behavioral assessment of LID in the 6-OHDA rat model of PD. Consistently with the need to standardize preclinical tools for anti-dyskinetic drug discovery, we propose a new, quick and reliable method for L-dopa induced AIMs assessment in the rat.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: Thomas Hartman Parkinson's Research Foundation

Title: Can a rat model of early, cognitive deficits in Parkinson’s disease and an open field task of visually cued home base formation help uncover the neurobiology of paradoxical kinesia?

Authors: *S. J. PERROTTA, Y. KIM, A. RODERICK, H. SODAWALLA, M. F. KRITZER
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Abstract: Parkinson’s disease (PD) is a neurodegenerative disorder characterized by cognitive as well as motor symptoms such as bradykinesia. Previous studies of a partial bilateral neostriatal 6-hydroxydopamine (6-OHDA) lesion rat model of early PD revealed striking abnormalities in the ways lesioned rats explored a Barnes maze, a paradigm typically used to measure spatial working and/or reference memory. Specifically, 6-OHDA rats spent extensive times investigating incorrect maze locations, often to the exclusion of wider exploration and successful location of the goal (Betancourt et al., Neuroscience ‘16). This could be due to impaired behavioral flexibility, e.g., perseveration, cognitive rigidity, similar to what is seen in ~ 20-30% of PD patients. However, this could also indicate that rats’ explorations were driven by external cues - in this case, incorrect goal locations, in some ways akin to paradoxical kinesia, wherein PD patients overcome bradykinesia by using external stimuli to guide movements. To explore this further, we tested 6-OHDA and control rats on a modified open field exploratory task. Specifically, rats were given one hour during their active period to freely explore a featureless 5 ft diameter table around which four distinct visual cues (large v. small/black v. white squares) were placed (1 ft from the edge, separated by 90 deg of arc). As expected, control rats quickly developed preferences for areas of the table adjacent to the cues; these were used as landmarks or home bases from which rats actively and widely explored the entire table surface. In contrast, the exploratory behaviors of the 6-OHDA rats were highly constrained. Thus, they quickly developed spatial preference for one of the cue sites and excursions from there corresponded

almost exclusively to retracing a path or pathways to and from another cue(s) location. When tested one week later, these group differences were even sharper and explorations of the 6-OHDA rats became even more constrained to cue location sites. Importantly, group differences do not appear to be explained by frank motor deficits as all rats performed similarly on a horizontal ladder test, moved in the open field with similar velocities and showed comparable levels of locomotion. Rather it seems plausible that in both Barnes maze and this open field paradigm 6-OHDA rats showed evidence of being stimulus bound. In addition to executive dysfunction/cognitive rigidity/behavioral inflexibility, the heavy reliance of 6-OHDA rats on external visual cues to guide exploration suggests that these may also be suitable models for understanding the neurobiological bases for paradoxical kinesia.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: NS059921

BNS Graduate Program

Title: Zolpidem alters L-DOPA-induced behavioral asymmetry in unilaterally 6-OHDA-lesioned rats

Authors: *R. ASSINI[1], E. D. ABERCROMBIE[2]
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Abstract: Presently, the most effective pharmacological intervention for Parkinson’s disease (PD) is dopamine (DA) replacement therapy, which requires administration of the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA). This intervention is initially effective, but debilitating side effects such as L-DOPA-induced dyskinesia (LID) commonly develop. Metabolic, immediate early gene, as well as *in vivo* neurophysiological studies have indicated that hyperexcitation within downstream nuclei of the basal ganglia (BG) circuit may be related to the emergence of LID-like behaviors. Interestingly, optogenetic and pharmacological inactivation of ipsilateral subthalamic nucleus (STN) have been shown to reduce LID-like behaviors in unilaterally 6-OHDA-lesioned rodents. Furthermore, surgical manipulation of either STN or internal globus pallidus (GPi) has also been shown to reduce LID in PD patients. Zolpidem acts

as a positive allosteric modulator of $GABA_A$ receptors, potentiating iPSCs with selectivity for the α_1 subunit. Within the BG, the α_1 subunit is expressed on projection neurons within external globus pallidus (GPe), STN, and BG output nuclei (substantia nigra pars reticulata/GPi). Given the overlap between the sites of successful interventions and the expression profile of the α_1 subunit within the BG, we hypothesize that zolpidem may serve as a novel pharmacological intervention for LID. As a result, we examined the effects of acute systemic administration of zolpidem on LID-like behaviors in unilaterally 6-OHDA-lesioned rats. We have devised a novel quantitative behavioral analysis that incorporates asymmetrical locomotor outputs (rotations/stereotypies) into a single asymmetry score. The validity of this measure was tested using a dose-response paradigm. Animals were pretreated with the peripheral aromatic L-amino acid decarboxylase inhibitor (AADC) inhibitor benserazide (15 mg/kg; i.p.) 30 min prior to L-DOPA (2.5, 5, 10, 25, or 50 mg/kg; i.p.) or saline, and behavior was recorded for 3 h. Rotational behavior and amount of time displaying dyskinetic stereotypies were quantified, and asymmetry scores were calculated. Our results indicate that our paradigm is indeed capable of discriminating between escalating doses of L-DOPA. Second, we utilized this analysis method to assay the effects of systemic zolpidem on L-DOPA-induced abnormal involuntary movements. Animals were pretreated and given L-DOPA (10 mg/kg; i.p.), as above, then given zolpidem (0.1, 0.5 mg/kg; i.p.) 40 min following L-DOPA. Preliminary results indicate that both doses of zolpidem abolish both rotational and LID-like behaviors in unilaterally 6-OHDA-lesioned rats.

Disclosures: R. Assini: None. **E.D. Abercrombie:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.06/V26

Topic: C.03. Parkinson’s Disease

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Deutsche Forschungsgemeinschaft DFG, WO 1732/4-1

Title: Ketamine reversed depressive-like behaviour and memory impairment but did affect vocal impairment in a rat model of Parkinson's disease

Authors: *R. ANDREATINI[1], D. D. VECCHIA[2], L. K. S. KANAZAWA[2], E. M. WENDLER[2], P. A. S. HOCAYEN[2], M. A. B. F. VITAL[2], R. N. TAKAHASHI[3], E. MIYOSHI[4], M. WÖHR[5], R. K. SCHWARTING[5]
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Abstract: Parkinson's disease (PD), a chronic neurodegenerative disease characterized by loss of nigrostriatal dopamine neurons, shows motor signals, including voice deficits (e.g. difficulties to articulate words and to keep the tone of voice), depression and memory impairment. Ketamine, an N-methyl-D-aspartate antagonist, has shown antidepressant effect in major depression and in animal models. Thus, the present study evaluated the actions of ketamine on depressive-like behaviours, memory impairment and ultrasonic vocalizations in rats with lesion of the *substantia nigra pars compacta* (SNc). Adult male Wistar rats received bilateral 6-hydroxydopamine (6-OHDA, 6 μg) or vehicle infusion bilaterally into the SNc and 21 days later they received vehicle (ip, once a week), ketamine (5, 10 and 15mg/kg, ip, once a week) or imipramine (20mg/kg, ip, daily) as a positive control, for 28 days. Before drug treatment, 6-OHDA treated rats showed gait impairments in the catwalk system, depressive-like behaviours (decreased sucrose preference and increased immobility in the forced swim test -FST), memory impairment (decreased social recognition of juvenile rat by adult rat), and decreases in the emission of 50-kHz ultrasonic vocalizations in response to fresh bedding (reduced call numbers, call durations, total calling time, and increased latency to start calling). In the FST, at lower doses, the anti-immobility effect of ketamine was associated with increased swimming (suggesting a serotonergic effect) while the higher dose of ketamine increased both swimming and climbing (indicating serotonergic and noradrenergic/dopaminergic effects, respectively). Ketamine also reversed anhedonia (reduction on sucrose preference), social memory and gait impairments but it did not affect impaired ultrasonic vocalization. Imipramine showed a similar profile. Both drugs also did not affect the 6-OHDA-induced reduction of tyrosine hydroxylase immunohistochemistry in the SNc, suggesting that they did not affect the lesion-induced loss of dopaminergic neurons. In conclusion, ketamine reversed depressive-like behaviour, social memory and gait impairments in an animal model of PD, indicating a promising profile for its clinical use in Parkinson's disease.

Disclosures: R. Andreatini: None. **D.D. Vecchia:** None. **L.K.S. Kanazawa:** None. **E.M. Wendler:** None. **P.A.S. Hocayen:** None. **M.A.B.F. Vital:** None. **R.N. Takahashi:** None. **E. Miyoshi:** None. **M. Wöhr:** None. **R.K. Schwarting:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

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NSF 0965983

Title: Changes in the cyclooxygenase pathway relevant to PGD2/J2 in a rat model of neuroinflammation exhibiting parkinsonian-like pathology

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Abstract: Prostaglandins are products of the cyclooxygenase pathway, and have emerged as important determinants of the cytotoxicity associated with neuroinflammation in Parkinson's disease (PD). However, their roles and mechanisms of action in neurodegeneration are poorly understood.
We previously established a rat model of neuroinflammation induced by the highly neurotoxic prostaglandin J2 (PGJ2), which is spontaneously derived from PGD2. PGD2 is the most abundant prostaglandin in the brain and increases the most under pathological conditions. PGJ2 was unilaterally injected into the right substantia nigra (SN) of adult Sprague Dawley male rats for two and four weeks (once per week). Compared to vehicle controls, the PGJ2-treated rats exhibited significant motor deficits concomitant with dose-dependent dopaminergic neuronal loss in the impaired SN.
To gain insight into the effect of PGJ2-induced neuroinflammation in this rat model, we performed immunohistochemical analyses to assess the distribution and changes of COX-2, Lipocalin-type PGDS (L-PGDS), Prostaglandin D receptor 2 (DP2) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in dopaminergic neurons, microglia and astrocytes in the SN, since these are key factors regulating the neurotoxic effects of PGD2/J2. L-PGDS is the synthase for PGD2. DP2 is a member of the class of PG receptors that binds PGD2 and PGJ2 with high affinity, resulting in decreased cAMP levels and increased intracellular calcium, therefore potentiating neuronal injury. 15-PGDH is a PG-inactivating enzyme which negatively regulates PG activity and converts PGD2 to its 15-oxo metabolites leading into inactive 13,14-dehydro-derivative. We also assessed the level of ubiquitinated proteins and phosphorylated α-synuclein at S129 (pSer129 α-syn) since PGJ2 can cause aggregation of proteins by interfering the normal function of proteasomes contributing to the pathogenesis of PD.
In conclusion, the PGJ2-induced rat model of neuroinflammation is highly valuable to identify and optimize therapeutics that suppress the neurotoxic effects of neuroinflammation mediated by the cyclooxygenase pathway.

Disclosures: **J. Ara:** 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.; Maria Figueiredo-Pereira. **C. Corwin:** 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.; Maria Figueiredo-Pereira. **M.E. Figueiredo-Pereira:** 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.; Maria Figueiredo-Pereira.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: CURE Grant

Title: The effect of hfe genotype on the progression of parkinson's disease in a mouse paraquat model

Authors: A. M. NIXON[1], E. NEELY[1], M. MEADOWCROFT[1], W. NANDAR[2], *J. R. CONNOR[1]
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Abstract: The HFE protein is critical in the regulation of cellular iron uptake. Mutations within this protein cause increased iron accumulation within parenchymal cells. One HFE mutation, H63D, has been shown to be increased in neurodegenerative diseases, such as Alzheimer’s Disease and amyotrophic lateral sclerosis (ALS); however, the relationship between the H63D HFE mutation and Parkinson’s Disease is not well known. To investigate this connection, we generated a mouse model in which the wild-type (WT) HFE gene is replaced by the H67D gene variant (mouse homologue of the human H63D gene variant). WT and H67D mice were given paraquat injections once a week for three weeks to induce Parkinson’s Disease. To assess the progression of Parkinson’s Disease, motor function was measured using a behavioral rotarod test. In addition, cellular and iron changes within the substantia nigra were measured by magnetic resonance imaging (MRI) and immunohistochemistry. The WT paraquat-treated mice had significantly more falls compared to the WT saline-treated group. However, there were no behavioral differences in the H67D paraquat- and saline-treated mice. The behavioral data corresponded to MRI analyses, which showed there were cellular changes within the substantia nigra of the WT paraquat-treated mice compared to their saline-treated counterpart. The H67D mice exhibited no significant cellular changes between treatment groups. To determine the cause of the observed cellular changes, immunohistochemistry was used to evaluate tyrosine hydroxylase levels, microglia, and astrocytes. We observed a significant increase in astrocytes within the substantia nigra of WT paraquat-treated mice compared to the control and H67D groups, but no significant differences were detected in tyrosine hydroxylase or microglia. These data suggest that the WT mice have an increased progression of Parkinson’s Disease compared to H67D mice which may be attributed to astrogliosis. Furthermore, the lack of changes within

the H67D paraquat-treated mice indicated that the HFE mutation may be protective against Parkinson's Disease.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

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Topic: C.03. Parkinson's Disease

Title: Transient impairment of *In vivo* burst firing in surviving dopamine neurons is associated with a temporary motor deficit after partial lesion

Authors: *L. KOVACHEVA, J. ROEPER
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Abstract: Parkinson disease (PD) is the second most prevalent neurodegenerative disorder and characterized the selective degeneration of vulnerable neuron populations, prominently among them, dopamine (DA) neurons in the substantia nigra (SN). It is currently unclear to what degree surviving DA SN neurons either homeostatically adapt their activity during PD to compensate for reduced population size and dopamine depletion or enter a functionally impaired state even before degeneration. To study the long-term temporal profile of post-lesional adaptations of the nigrostriatal DA system, we utilized a unilateral partial 6-hydroxydopamine (6-OHDA) model. By monitoring spontaneous motor behavior of the 6-OHDA and ACSF-infused control mice for 3 month post-surgery, we identified two distinct phases. As expected, the 6-OHDA infused mice displayed a strong contralateral turning deficit compared to ACSF-infused mice during the first few weeks (impaired phase). However, over the course of 2 months this turning deficit completely disappeared (recovered phase). To compare the functional activities of surviving DA SN neurons during these two behavioral states, we carried out in vivo single unit extracellular recordings combined with juxtacellular labelling for immunohistochemical und morphological characterization. By focusing on the medial SN, we found that the firing frequencies and patterns of surviving DA neurons recorded during the recovered phase were not significantly different from DA SN neurons from ACSF-infused controls. In contrast, the activity of DA SN neurons from 6-OHDA infused mice recorded during the earlier impaired phase, displayed a significant 7-fold reduction in burst rate (control: 0.31 ± 0.14, n=9; 6-OHDA: 0.04Hz ± 0.02, n=9), while their mean frequency of firing was not affected (control: 5.4Hz ± 0.51, n=9; 6-OHDA: 4.13Hz ± 0.59, n=9). We are currently investigating the possibility of a causal role of the temporary reduction of burst rate in surviving DA SN neurons for the impaired turning behavior.

Disclosures: **L. Kovacheva:** None. **J. Roeper:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: PAPIIT IN204715

PAPIIT IN207116

Title: Chronic nicotine administration improves L-DOPA-induced dyskinesia in rats and reduces the expression of FosB in the dorsal striatum

Authors: ***A. GOMEZ**[1], M. PALOMERO-RIVERO[1], D. MILLÁN-ALDACO[1], M. GUERRA-CRESPO[1], Y. TIZABI[2], R. DRUCKER-COLÍN[1]
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Abstract: Dopamine (DA) precursor L-3,4-Dihydroxyphenylalanine (L-DOPA) remains the most effective symptomatic treatment of Parkinson’s disease (PD), which is primarily due to damage or dysfunction of the nigrostriatal dopaminergic pathway. However, long-term administration of L-DOPA induces the development of abnormal involuntary movements known as L-DOPA induced dyskinesia (LID), which can severely handicap the patient. Mechanisms underlying LID are not fully understood and its medical treatment is generally unsatisfactory. Neuroprotective effects of nicotine and its amelioration of LID in primate animal models of PD have been reported. In this study, we sought to determine whether nicotine may also reduce LID in a rat model of PD and whether this effect might be associated with a reduction of striatal FosB. Increased FosB in the dorsal striatum would be reflective of increased immediate early gene expression, which is not only considered a marker of dyskinesia, but may be causally related to LID. Adult male Wistar rats were stereotaxically injected with 6-OHDA in the substantia nigra pars compacta (unilaterally) to induce PD-like symptoms (e.g. rotational movements). These rats were then exposed to nicotine via drinking water (30 mg/l) for 3 weeks after which they were treated daily for 4 weeks with L-DOPA (8 mg/kg i.p) followed by another 4 weeks of L-DOPA (12 mg/kg i.p.). Nicotine concentration in the water was maintained for the entire period in these animals. Controls were treated identically, except no nicotine was present in the water. Our findings indicate that animals exposed to nicotine had significant abatement of dyskinesia as well as better performance in the beam test. The improvement in motor function was associated with a significant reduction in FosB expression in the dorsal striatum. Together,

our results provide further support for therapeutic potential of nicotine in LID and suggest that this beneficial effect may be at least partially related to a reduction in dorsal striatal FosB.

Disclosures: A. Gomez: None. **M. Palomero-Rivero:** None. **D. Millán-Aldaco:** None. **M. Guerra-Crespo:** None. **Y. Tizabi:** None. **R. Drucker-Colín:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

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Title: MitoPark mouse recapitulates depression and anxiety behaviors underlying Parkinson’s disease

Authors: *A. G. KANTHASAMY, M. R. LANGLEY, S. GHAISAS, M. AY, H. JIN, V. ANANTHARAM, A. KANTHASAMY
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Abstract: The main pathophysiological processes of Parkinson’s disease (PD) are mainly attributed to motor deficits, but it has recently been recognized that PD is associated with a high rate of non-motor neuropsychiatric comorbidities, including depression, that often precede the onset of motor deficits and significantly reduce the quality of life. The neurocognitive mechanisms underlying depression in PD are unclear and treatment is suboptimal. Unfortunately, although a few animal models recapitulate some of the non-motor symptoms, they still do not mimic the major non-motor symptoms such as depression, anxiety and cognitive abnormalities seen in PD. The MitoPark mouse, a transgenic model of mitochondrial impairment recently developed by specific inactivation of TFAM in dopaminergic neurons, spontaneously exhibits progressive motor deficits and neurodegeneration, recapitulating several features of PD including therapeutic response to L-DOPA. We characterized the clinically relevant motor and non-motor symptoms in MitoPark mice during the course of 8-24 wks of disease progression relative to littermate controls. Motor deficits in MitoPark mice begin around 12 wks and become severe by 16-24 wks. Interestingly, male MitoPark mice showed spatial memory deficits before female mice, beginning at 8 wks and becoming most severe at 16 wks, as determined by Morris water maze. MitoPark mice exhibited olfactory deficits in novel and social scent tests as early as 10-12 wks. MitoPark mice between 16-24 wks spent more time immobile in forced swim and tail

suspension tests, and made fewer entries into open arms of the elevated plus maze, indicating depressive- and anxiety-like phenotypes, respectively. Importantly, the well-known antidepressant desipramine significantly reversed the depressive behavior in both male and female MitoPark mice. Collectively, our results indicate that MitoPark mice progressively exhibit deficits in cognitive learning and memory, olfactory discrimination, and anxiety- and depressive-like behaviors. Thus, the MitoPark mouse is a valuable model for studying depression and anxiety behaviors underlying non-motor deficits in PD pathology and for testing novel therapies targeting non-motor deficits of PD.

Disclosures: A.G. Kanthasamy: None. **M.R. Langley:** None. **S. Ghaisas:** None. **M. Ay:** None. **H. Jin:** None. **V. Anantharam:** None. **A. Kanthasamy:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: NIH NS083498

Title: Mfn2 overexpression attenuates MPTP neurotoxicity *In vivo*

Authors: *F. ZHAO, X. ZHU
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Abstract: Mitochondrial dysfunction represents a critical event in the pathogenesis of Parkinson’s disease (PD). Increasing evidence suggested the involvement of disturbed mitochondrial fission/fusion dynamics and quality control in the mitochondrial dysfunction in PD. Indeed, our previous study demonstrated that MPP^+ induced mitochondrial fragmentation *in vitro* which plays a critical role in mediating MPP^+-induced mitochondrial abnormalities and cellular dysfunction in both SHSY-5Y neuroblastoma cells and primary midbrain neurons. In this study, we aimed to assess whether blocking MPTP-induced mitochondrial fragmentation by overexpressing Mfn2 affords neuroprotection *in vivo*. We found that the significant loss of dopaminergic neurons in the substantia nigra (SN) induced by MPTP treatment as seen in the wild type littermate control mice was almost completely blocked in mice overexpressing Mfn2 (hMfn2 mice). A dramatic reduction of dopamine neuronal fibers in striatum caused by MPTP administration was also partially inhibited in hMfn2 mice. MPTP-induced oxidative stress and inflammatory response in SN and striatum was significantly alleviated in hMfn2 mice. At last, the impairment of motor function caused by MPTP was also blocked in hMfn2 mice. Overall, our work demonstrated that restoration of mitochondrial dynamics by Mfn2 overexpression

protects against neuronal toxicity in MPTP-based PD mouse model which supports the modulation of mitochondrial dynamics as a potential therapeutic target for PD treatment.

Disclosures: F. Zhao: None. **X. Zhu:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

Support: Weston Foundation

Title: Inflammation in the gut of a new progressive rat model of PD

Authors: G. CHING[1], Y. OBAYASHI[2], M. MEJIAS[2], R. KORNELSEN[2], J. VANKAMPEN[3,4], J. O'KUSKY[2], *D. J. DOUDET[2]
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Abstract: Pathophysiology of the gastrointestinal tract is increasingly being explored as a possible means to diagnose and to measure the progression of Parkinson's Disease (PD). While the presence of Lewy bodies is seen as the primary marker of neurodegenerative disease-related gut pathophysiology, recent publications theorize that gut inflammation may serve as a reliable indicator and precipitating condition of PD as well (1). A previous study using human biopsies failed to find a "significant difference in the expression of pro-inflammatory cytokines or glial marker between patients with and without enteric Lewy pathology" (2). However, it has been suggested that the fact that biopsies take only a small highly localized sample of gut tissue causes results derived from these samples to be unrepresentative of overall pathophysiology. To explore the hypothesis that gut inflammation is a reliable indicator of PD, we run a small pilot experiment: the gut of 6 experimental BSSG-induced PD rat (a novel progressive rodent model of PD (3)) and of 4 control rat were prepared as swiss rolls, paraffinized, sectioned, and immunohistochemically stained using an anti-CD-68 primary antibody and a goat anti-mouse secondary antibody visualised using Vector Red. Preliminary results demonstrated that elevated inflammation was present in the submucosa in the colon of all six experimental rats in comparison to only one out of four control rats. These data support further exploration of increased inflammation of gut submucosa in PD as well as in this novel progressive rodent model of PD. Further experiments to evaluate the colonic colocalization of synuclein aggregates with CD68 in BSSG rat model are ongoing in larger subgroups. These data further support the hypothesis that gut submucosa inflammation is indicative of PD development as much as brain

inflammation. This will be a first step to map the progression of inflammation in the gut along the timeline of the development of other pathophysiological symptoms. 1)Houser & Tansey, Parkinson's Disease, 2016 2) Devos et al., Neurobiology of Disease, 2013 3) VK et al. PLOS one, 2015

Disclosures: G. Ching: None. **Y. Obayashi:** None. **M. Mejias:** None. **R. Kornelsen:** None. **J. VanKampen:** A. Employment/Salary (full or part-time):; Neurodyn Life Science. **J. O'Kusky:** None. **D.J. Doudet:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

Support: DST No: SR/SO/HS-121/2012 to Dr. PAA

Title: Postnatal developmental apoptosis in mice strains and its differential susceptibility to MPTP in adulthood

Authors: *Y. HAOREI[1], D. J. VIDYADHARA[1], C. SAGAR[2], T. R. RAJU[1], P. A. ALLADI[1]
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Abstract: Different ethnic populations worldwide are known to have differential prevalence of Parkinson's disease.There are reports of varying dopaminergic (DA) neuronal numbers across races with the ethnic groups with lower nigral neuronal counts having higher incidence of PD. Similarly, mice strains with fewer DA neurons are highly susceptible to MPTP than the strains with more nigral neurons. It is yet not known whether developmental apoptosis has a role in determining the basal DA neuronal numbers and the differential susceptibility. We therefore used two different strains of mice with differential susceptibility to MPTP. Their F1 crossbreds were studied as experimental model to understand the phenomenon of admixing.
We looked at the dopaminergic neurons in C57BL/6J and CD-1 mice and their F1 crossbreds with respect to early postnatal apoptosis in the midbrain substantia nigra pars compacta (SNpc) including apoptotic factors such as Bax, Bcl-2, AIF and caspase-3. MPTP-induced ultra-structural changes in the mitochondria were studied at adulthood. The MPTP-susceptible C57BL/6J showed prolonged developmental apoptosis and harbored higher basal apoptotic markers than the MPTP-resistant CD1. The crossbreds showed expression patterns similar to or better than CD1. Similar results were observed in the mitochondrial integrity of adult mice where the changes in the susceptible C57BL/6J strain were more severe than the resistant CD1 or their crossbreds. Thus, the developmental expression of apoptotic markers appears to be important

determinants governing the numbers and mitochondrial functionality may govern the baseline susceptibility of dopaminergic neuron at adulthood. This study provides interesting lead to understand the pathophysiology of Parkinson's disease

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

Title: Oscillatory signatures of L-DOPA-induced dyskinesia are not reduced by ketamine

Authors: *T. YE[1], M. J. BARTLETT[2], T. FALK[2], S. L. COWEN[3]
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Abstract: A recent clinical case study from our group suggests that sub-anesthetic ketamine infusions (0.15 - 0.3 mg/kg/hr for 72 hrs) reduces L-DOPA induced dyskinesias (LID) in human patients with Parkinson's disease (Sherman et al., 2016), and in a rodent model of LID (Bartlett et al., 2016). Although the mechanisms underlying ketamine's therapeutic effects are not known, LID and other disorders treated with ketamine are associated with hypersynchronous oscillatory activity in the cortex and striatum. This suggests that hypersynchronous interactions between brain regions contributes to the pathology. Because LID is associated with synchronous high gamma oscillations (70 - 110 Hz) in the motor cortex (Halje et al., 2012), we hypothesized that repeated ketamine injection would reduce power in this frequency band following L-DOPA administration. To test this hypothesis, we used an animal model of LID whereby 6-OHDA-lesioned rats were primed for 21 d with 7 mg/kg of L-DOPA. Animals (n = 7) with a cumulative forelimb, axial, and orolingual abnormal involuntary movements (AIMs) score of 33.6 ± 6.6 (mean ± SD) were then implanted with electrode arrays that targeted motor cortex (AP +1.28, ML +2.2, DV -1.4), striatum (AP +1.28, ML centered +2.7, DV -4.6 to -6.8) and hippocampus (AP +3.0, ML centered -2.2, DV -1.4 to -3.8). Data from this group were compared with data collected from control (n = 6) and 6-OHDA (n = 6) rats. Neural recordings were acquired continuously over an 11-hour period during which animals were administered five ketamine (20 mg/kg every 2 hrs, total of 5 *i.p*. injections) or saline injections. This injection protocol was previously shown to reduce AIMs in an animal model of the disease (Bartlett et al., 2016). LID was induced on the 5th injection by pairing the ketamine or saline injection with an injection of L-DOPA (7 mg/kg, *i.p.*). We observed that L-DOPA increased low- and high-gamma band (> 40 Hz) activity in motor cortex relative to saline injection; however, contrary to our original hypothesis, treatment with ketamine did not reduce oscillatory power in this band during the 92 -

110 min post-injection interval *(p*=0.99). Furthermore, although the LID rats used in this study met criteria of AIM scores, they did not exhibit the focal 80 Hz oscillatory increase previously observed in other animal studies. This may be due to the lower dosage of L-DOPA used here. The observation that ketamine did not reduce L-DOPA induced gamma-band activity suggests that the mechanisms underlying ketamine's therapeutic benefit may not involve the reduction of oscillatory hypersynchrony in motor cortex.
Keywords: L-DOPA, Parkinson's disease, gamma

Disclosures: T. Ye: None. **M.J. Bartlett:** None. **T. Falk:** None. **S.L. Cowen:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

Title: Allosteric modulation of NMDA receptors rescues impaired synaptic plasticity and behavioural impairment in experimental Parkinsonism

Authors: *M. NOUHI
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Abstract: The GluN2 subunits that compose NMDA receptors (NMDARs) are attractive drug targets for therapeutic intervention in Parkinson's disease (PD). We recently found that the protein levels of GluN2D and the functions of GluN2D-containing NMDARs are altered in the striatum of a mouse model of PD [1] and that a positive allosteric modulator of NMDARs containing GluN2C or GluN2D subunits, CIQ * [2], promoted the release of dopamine in the partially dopamine-depleted striatum [3].
We now found that in corticostriatal brain slices from 6-hydroxydopamine(6-OHDA)-lesioned mice, perfusion with CIQ reversibly depressed glutamatergic synaptic transmission in the dopamine-depleted striatum and had no effect in the intact striatum. This depressant action was mediated through a presynaptic mechanism and might counteract the increased glutamatergic transmission in the dopamine-depleted striatum demonstrated in earlier studies. We also examined the effect of CIQ on the induction of a dopamine- and NMDAR-dependent form of synaptic plasticity, i.e. long-term potentiation (LTP). LTP in the striatum is believed to underlie motor learning and is impaired in experimental Parkinsonism. We found that in the dopamine-depleted striatum perfusion with CIQ rescued impaired LTP. Moreover, acute and sub-chronic (7 days) intraperitoneal injections of CIQ also rescued impaired LTP in the dopamine-depleted striatum without affecting LTP in the intact striatum.
Knowing the significant impact of plasticity on motor behavior and learning, we then investigated the effect of CIQ on the behavior of lesioned mice. One of the early behavioral

phenotypes developed in 6-OHDA lesioned mice is forelimb asymmetry. Using 10mg/kg i.p. injection of CIQ sub chronically (7 days), we found a positive effect on the asymmetry. Indeed, 6-OHDA lesioned mice that received a 7 days treatment with CIQ demonstrate a significant improvement in using both paws as compared with vehicle-treated mice.
Our results demonstrate that CIQ rescues neurophysiological and behavioral impairments in experimental Parkinsonism and suggest that allosteric modulators of GluN2D-containing NMDARs might be valuable therapeutic tools for the management of PD.
* CIQ: ((3-chlorophenyl) (6,7-dimethoxy-1-((4-methoxyphenoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone)

Disclosures: M. Nouhi: None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.17/W11

Topic: C.03. Parkinson's Disease

Title: The potent and selective A_{2A} receptor antagonist, preladenant, produces a robust effect in L-dopa induced turning, but only modest efficacy in the cylinder assay in unilaterally 6-OHDA lesioned rats

Authors: A. C. MORSE[1], *R. HODGSON[2], R. O. PUSSINEN[2], J. KORKALAINEN[2], M. SUHONEN[2], A. J. NURMI[2], J. A. VIVIAN[3]
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Abstract: A_{2A} receptor antagonists represent one of the most studies novel symptomatic treatments for Parkinson's disease (PD) over the past several decades. Multiple A_{2A} receptor antagonists consistently produce robust activity in animal models such as reversal of haloperidol-induced catalepsy and potentiation of L-dopa induced rotations in unilaterally 6-OHDA lesioned rats. However, those robust positive data in non-clinical models have not translated into robust clinical efficacy. Preladenant (2-(2-Furanyl)-7-[2-[4-[4-(2-methoxyethoxy)phenyl]-1-piperazinyl]7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrmidine-5-amine) and istradefylline represent structurally distinct A_{2A} receptor antagonists that have been tested in multiple clinical trials and the drugs have had mixed, with the most recent result a failed Phase III study with preladenant. Here we hypothesize that the disconnect between the animal and clinical results was that the majority of the animal assays relied on an increase in motor activity, which is something that A2A receptor antagonists induce in rodents whereas there is no evidence of A_{2A} antagonist induced hypoactivity in human studies. To test this hypothesis, we assessed the effect of preladenant (3 mg/kg, PO) in unilaterally medial forebrain bundle 6-OHDA lesioned rats in L-

dopa induced turning and the cylinder test. Consistent with our hypothesis, we found that while we were able to replicate previously published findings that preladenant robustly potentiates L-dopa induced turning, but it only had a modest effect in the cylinder test, a functional assay, that failed to achieve statistical significance. This discrepancy highlights the importance of including functional readouts in preclinical studies of novel symptomatic PD candidates.

Disclosures: **A.C. Morse:** A. Employment/Salary (full or part-time):; Dart Neuroscience. **R. Hodgson:** A. Employment/Salary (full or part-time):; Charles River Discovery. **R.O. Pussinen:** A. Employment/Salary (full or part-time):; Charles River Discovery. **J. Korkalainen:** A. Employment/Salary (full or part-time):; Charles River Discovery. **M. Suhonen:** A. Employment/Salary (full or part-time):; Charles River Discovery. **A.J. Nurmi:** A. Employment/Salary (full or part-time):; Charles River Discovery. **J.A. Vivian:** A. Employment/Salary (full or part-time):; Dart Neuroscience.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

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Topic: C.03. Parkinson’s Disease

Support: R01AG043467

Title: Late aging influences on L-DOPA-induced dyskinesia in the hemi-parkinsonian rat

Authors: *K. E. LANZA, A. PERKINS, T. DEAK, C. BISHOP
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Abstract: Parkinson’s Disease (PD) is a neurodegenerative disorder characterized by nigro-striatal dopamine (DA) cell loss resulting in pronounced motor deficits. DA replacement therapy via the DA precursor L-DOPA initially reduces motor symptoms, but eventually patients experience loss of treatment efficacy and develop L-DOPA-Induced Dyskinesia (LID) characterized by abnormal involuntary movements (AIMs). Multiple factors contribute to PD incidence and LID development. For PD incidence, age is perhaps the greatest risk factor. Clinical research suggests that age of disease onset also differentially predicts both therapeutic outcomes and motor complications such as LID, with “early onset” patients being most at risk. However, recent experimental evidence in 6-hydroxydopamine (6-OHDA) lesioned mice showed that those administered L-DOPA treatment in later adulthood with more recovery time (12 or 24-month) displayed less severe LID than those commencing L-DOPA treatment at a younger age (3-month). Therefore, it is unclear whether age or the interval between DA loss and L-DOPA initiation is the most predictive of LID development. Given established differences between young and aged brain and the paucity of experimental work in aged PD models, the present study

aimed to isolate the influence of late aging on initial LID manifestation. To this end, young (3-month) and old (18-month) male Fischer 344 rats received either a unilateral 6-OHDA or sham lesion of the medial forebrain bundle. Seven days after surgery, rats were tested for off-treatment motor-deficits using the Forepaw Adjusting Steps (FAS) test. Both 3-month and 18-month rats displayed similar motor impairment due to DA depletion. Rats received an acute injection of L-DOPA (6 mg/kg) 2-4 days later and AIMs were monitored following injection for a 3-hour period. Clear age-dependent differences emerged in LID expression, with lesioned 18-month old rats displaying significantly higher AIMs, both in terms of intensity and trajectory when compared to lesioned 3-month rats. Rats were killed off-treatment 7 days later and striatal tissue was collected for analysis of monoamines via high performance liquid chromatography. Results indicated that lesioned 3-month and 18-month rats had similar depletion of both striatal DA and DOPAC, suggesting that differential responses to L-DOPA were not explained by differences in lesion severity. These data suggest unique, age-dependent mechanisms that contribute to the incidence of LID and by extension implicate novel avenues for LID management.

Disclosures: K.E. Lanza: None. **A. Perkins:** None. **T. Deak:** None. **C. Bishop:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: NIH/NIDA DA034783

Title: Behavioral adaptations in parkin knockout rats support the role of parkin in Parkinson's disease pathology

Authors: *A. SHARMA[1], S. P. CALLAN[2], A. HARUTYUNYAN[1], T. A. GORE[3], S. A. PERRINE[3], A. MOSZCZYNSKA[1]
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Abstract: Parkinson’s disease (PD) is a common neurodegenerative disorder mostly idiopathic in origin; however, several genes have been identified to play a role in PD pathology. One such gene is *PARK2*, which encodes for the protein parkin, an E3 ubiquitin ligase responsible for proteasomal-dependent degradation of misfolded or damaged proteins. Several rodent parkin knockout (PKO) models have been developed to assess the role of parkin in PD pathology; however, the primary limitation of these models is that animals lacking parkin do not show locomotor impairments observed in humans with PD. Despite this fact, parkin remains under investigation in PD research as PKO mice manifest some of the non-motor characteristics of PD

such as increased anxiety-like behavior and cognitive impairments. Available literature data suggests that monoamine oxidase B (MAO-B), which is a target for many pharmacotherapeutics currently approved for treating PD, may be responsible for the observed non-motor characteristics in PKO mice. Additionally, literature data suggests that a loss of parkin increases MAO-B activity. In contrast, our lab determined that the deletion of the *PARK2* gene in rats caused a decrease in MAO-A and B activity. Given that loss of MAO-A/B may decrease anxiety-like behavior and improve cognitive memory, we hypothesized that PKO rats would display a decrease in anxiety-like behavior and an increase in recognition memory. Anxiety-like behavior in young adult male Long-Evans wild type (WT) rats and PKO rats was assessed using the open field test (OFT), the elevated plus maze (EPM) test, and the light/dark box (LDB) test. Short-term memory was assessed using the novel object recognition (NOR) test. Compared to the WT rats, the PKO rats displayed increased preference for the center square during the second OFT trial ($p < .05$) and increased open arm exploration during the EPM test ($p < .01$). They also showed significantly decreased dark-side exploration during the LDB test ($p < .01$). During the NOR test, PKO rats displayed increased preference for the novel object from acquisition to testing ($p <. 05$); however, upon retesting one week later, there was no effect of genotype, time, or time by genotype interaction (p values = 0.95, 0.43, and 0.37, respectively). In summary, we found that the PKO rats are less anxious and possess better short-term memory than the WT rats, suggesting that PKO rats, unlike PKO mice, functionally adapt to the loss of parkin, at least in part, by decreasing MAO-A/B activity. *Support: NIH/NIDA DA034738*

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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CNPq

Title: Role of tetrahydrobiopterin pathway in nociceptive responses in rats following intranasal MPTP administration, an animal model of Parkinson´s disease

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Abstract: Pain and sensory abnormalities are present in a large proportion of Parkinson's disease (PD) patients and have a significant negative impact in quality of life. However, the mechanisms responsible for this symptom are not well understood. Therefore, my current research aims to better elucidate the mechanisms involved in altering nociception observed in patients with PD. Previous studies demonstrated increased tetrahydrobiopterin (BH4) levels in the brain of PD patients and that BH4 overproduction in sensory neurons increases pain sensitivity in humans and animal models. Therefore, this study aimed to evaluate nociceptive response in rats following intranasal (i.n.) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an animal model of early stages of PD, and the effects of inhibition of BH4 synthesis by sulfasalazine (SSZ). Firstly, 16 male Wistar rats (90 days) were treated with a single i.n. infusion of MPTP (1 mg/nostril) or saline and their nociceptive response were evaluated in von Frey and hot plate tests at 3, 7, 14 and 21 days later. Next, we investigated whether MPTP-induced nociception can be modulated by BH4 pathway. For this, 32 male Wistar rats (90 days-old) were administered with a single i.n. infusion of MPTP (1 mg/nostril) or saline and 14 days later their nociceptive responses were evaluated in the von Frey and hot plate tests. After that, the animals were treated with sulfasalazine (50 mg/kg) or vehicle by gavage twice a day during 3 days. Von Frey and hot plate tests were performed at 0, 1, 2 and 3 h, and open field (OF) test 1.5 h after the last SSZ administration (CEUA PP830/2012). Our results indicated that MPTP induced mechanical and hot hyperalgesia at 14 and 21 days after i.n. infusion. The SSZ treatment reduced MPTP-induced hot and mechanical hyperalgesia at 1 and 2 h after the last drug administration. None treatment altered the locomotor activity of animals in the OF. This study provides the first evidence that intranasal MPTP, an experimental model of early PD, induced nociception in rats. Moreover, this study provides evidence that inhibition of BH4 synthesis is able to reduce MPTP-induced hyperalgesia in rats. These findings indicate the potential role of BH4 pathway on mechanisms involved in the pain symptoms in PD.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson's Disease

Support: NIH

Title: Multiscale network analysis reveals novel targets in Parkinson's disease

Authors: *Q. WANG, M. WANG, W.-M. SONG, P.-Y. PAN, Y. ZHANG, B. ZHANG, Z. YUE
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by selective vulnerability of dopaminergic neurons in substantia nigra and accumulation of alpha-synuclein in Lewy Bodies in affected brain regions with manifestation of both motor and non-motor syndromes. Previous genetic studies have discovered ~20 PD causal genes and ~30 PD-associated loci with diverse biological functions. However, these genetic variants only account for ~10% of total PD cases. The majority of PD cases are sporadic and the disease etiology remains poorly understood. To address the complexity of PD, we employed a multiscale network biology approach to a large cohort as a combination of multiple gene expression studies of postmortem human brains in PD and normal control. We constructed gene co-expression and causal networks in PD and identified key drivers of a neuron-specific and synaptic transmission enriched subnetwork, which is highly associated with PD. We experimentally validated the role of the top driver in PD pathogenesis. pHluorin-based quantitative imaging analysis showed that shRNA-mediated knockdown of this driver gene in wildtype mouse midbrain cultures led to impaired endocytosis as well as exocytosis, suggesting its involvement in vesicle recycling. *In vivo* knockdown of the driver gene in mouse model by AAV injection demonstrated impaired locomotor functions. Further pathological evidences revealed that there was a loss of TH+ neurons in the substantia nigra of the mutant mice with knockdown of the key driver gene, validating *it* as a key causal regulator in PD. Our multiscale network analysis not only reveals the global gene-gene interaction and regulation structures, but also pinpoints key causal regulators underlying PD, thus paving a way towards a holistic understanding of the molecular mechanisms underlying PD and facilitating the discovery of novel therapeutics for PD.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Support: NSF Grant 1351112

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Title: Behavioral and electrophysiological assessment of gradual dopamine depletion in the rat

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Abstract: Parkinson's disease (PD) is a debilitating motor disorder characterized by a progressive loss of dopaminergic neurons. With the progression of pathology, patients experience increasing severity of motor and psychiatric deficits that encompass, bradykinesia, tremor, and impulsivity. Pathologically robust beta oscillations (~12-20 Hz in humans; ~15-35 Hz in rodents) are common in humans and rodents with parkinsonism, but the contributions of synchronous beta activity to symptom severity are not understood. Typical animal studies induce PD-like symptoms with a single, large volume injection of 6-hydroxydopamine (6-OHDA) that entirely depletes dopamine (DA) expression within a short period of time. Though this approach provides insight on the pathological effects of complete DA loss, it constitutes a non-progressive model of an inherently progressive disease. To examine the prodromal stages of PD, recent studies have demonstrated that repeated low-dose injections of 6-OHDA correlate with gradual DA depletion in the mouse. However, the behavioral and electrophysiological deficits associated with the decline in DA levels have not been well characterized in the rat, a preferred model for behavioral and electrophysiological studies of PD. In the present study, we gradually depleted DA expression in the rat by administering bilateral, low-dose intracranial injections of 6-OHDA to the medial forebrain bundle. One week following each injection, rats performed behavioral tasks to assess parkinsonian severity. Open field exploration quantified general locomotor skills and a pasta handling task quantified fine motor skills. Rats were sacrificed for histological assessment of DA depletion at the end of the study. Results from the pasta handling task suggest that small dose 6-OHDA injections can correlate with deficits in fine motor behavior. However, distinctive changes in general locomotor behavior were not observed until DA was depleted entirely. Furthermore, local field potential (LFP) recordings over motor cortex reveal a manifestation of beta oscillations with changes in DA expression. These results suggest that deficits in motor behavior with progressive DA depletion may manifest first in fine motor coordination and that changes in electrophysiological profiles may correlate with DA expression. Future studies will analyze gait and step parameters with refined motor behavior tasks being developed by our lab. Additionally, the model described here could be utilized to investigate the three-way relationship between progressive loss of DA, electrophysiological activity of neural processing, and parkinsonian motor symptom severity.

Disclosures: H.Y. Febinger: None. **C.M. Henry:** None. **A.D. Dorval:** None.

Poster

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Topic: C.03. Parkinson's Disease

Support: Ed Rudman Foundation

NIH Grant NS079623

Title: Quantifying gait asymmetries in mouse models of Parkinson's

Authors: *L. BROOM[1,2], A. WORLEY[1], V. VANDERHORST[2,1]
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Abstract: Gait problems are common in the setting of Parkinson's disease (PD), and can manifest in multiple ways. One of these includes asymmetries which are apparent from observation and may be related to more pronounced bradykinesia and/or rigidity on one side compared to the other. Available PD mouse models represent these features to variable degrees, but asymmetries of spatial and/or temporal gait measures have received little attention. Previously, we have reported a method that allows translation of speed dependent gait metrics between mice and humans. Here we develop this further to capture spatial and temporal asymmetries using models that cause an asymmetrical or symmetrical loss of dopamine neurons. To induce Parkinsonism, 6-hydroxydopamine (6-OHDA) was injected in the substantia nigra resulting in unilateral cell loss or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered subcutaneously resulting in bilateral cell loss. Gait videos were obtained in mice prior to and following loss of dopamine neurons using a high speed camera and runway. Gait metrics were calculated from video frames in MATLAB and analyzed using Graphpad prism. Step length is defined as the distance between the position of one foot and next similar position of the opposite foot. Step length values were plotted as a function of speed, capturing the velocity range of walking. We used a best-fit regression model to compare left and right limbs in pre and post-lesion conditions. Spatial alternation is defined as the ratio of step length to stride length of the opposing limb, whereas temporal alternation is defined as the relative timing of opposing paws. Both measures are represented as scores between 0 and 1, with a score of 0.5 corresponding to perfectly even alternation. Alternation scores were assessed statistically using circular statistics (Watson-Williams) to detect shifts in spatial or temporal patterns of foot placement and Rayleigh to determine uniformity of data. Compared to control, the unilateral 6-OHDA model induced a difference between left and right step length measured as a function of speed. Complementing these measures were changes in spatial, but not temporal alternation. We did not find differences in speed dependent step length or changes in spatial or temporal alternation in the bilateral MPTP model. These data indicate that circular statistics and left-right differences in step length can be used to objectively quantify changes in spatial and temporal asymmetries of gait metrics. This method provides a powerful tool to study clinically relevant mouse models, and provides translational opportunities for gait disorders in patients, including those with PD.

Disclosures: L. Broom: None. **A. Worley:** None. **V. Vanderhorst:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: NIH Grant 1F31NS093944

Title: Progression of SNr pathophysiology depends on mouse model of dopamine depletion

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Abstract: Parkinson's disease (PD) is characterized by the progressive loss of dopamine in the basal ganglia that drastically alters circuit physiology and ultimately motor function. During normal aging in humans, dopamine levels depreciate during late stage adulthood (55-80 years old) by 1% and lead to no attributable deficits in function. In contrast, dopamine levels in individuals with PD depreciate at the rate of ~11% over the course of 10-20 years where motor deficits do not appear until ~80% of dopamine is lost. Animal models are critical to our understanding of the pathophysiology and potential treatment of neurological disorders, including PD. The most difficult component of PD to recapitulate in animal models is the progressive nature of dopamine loss that results in end-stage motor symptoms. Our goal is to determine whether the time course of dopamine depletion and the model used affects progression and end-stage pathophysiology differentially. Our hypotheses are as follows: (1) end-stage pathophysiology will be less severe when dopamine loss occurs more gradually, given the system's ability to compensate to gradual, but not acute, dopamine loss and (2) the presence of pathological alpha-synuclein inclusions will cause more severe pathology earlier during the progression of dopamine loss than in a standard neurotoxin model. In this study, we compared the neural activity within the substantia nigra pars reticulata (SNr) of awake head-restrained mice that had undergone dopamine depletion using the following protocols: (1) injection of pre-formed fibrils of alpha-synuclein bilaterally into the striatum, (2) injection of 6-hydroxydopamine (6-OHDA) bilaterally in the medial forebrain bundle (MFB) acutely or (3) gradually over a month, (4) one month after acute, unilateral 6-OHDA injection into the MFB. We observed a decrease in firing rate across all dopamine depletion models. Interestingly, we also observed different proportions of regular, irregular, and bursting firing patterns found within the SNr depending on the model, with gradual depletions resulting in a greater number of irregular firing patterns and bilateral acute depletion resulting in a greater number of bursting firing patterns. This study provides fundamentally important findings that clearly identify

differences in animal models significant to interpretation and application of clinically relevant investigations.

Disclosures: A.M. Willard: None. **K.J. Mastro:** None. **A.H. Gittis:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Title: Evaluation of constipation endpoints in MPTP-treated mice

Authors: *R. O. PUSSINEN, A. J. NURMI, R. HODGSON
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Abstract: Parkinson’s disease (PD) it typically characterized as a movement disorder and the vast majority of animal models have concentrated on recapitulating motor disturbances. Recently, there has been an increasing recognition of the importance of non-motor symptoms in PD and animal models designed to test the efficacy of putative treatments. Constipation is one of the most prevelant non-motor symptoms in PD and a recent finding demonstrated that MPTP (15 mg/kg i.p. twice per day on day -1 and 0; total 60mg/kg MPTP) treated mice have reduced stool frequency relative to non-MPTP treated mice (Ellet et al., 2016). The purpose of the present work was to assess constipation in MPTP-treated mice by measuring colon motility and fecal output. Colon motility was assessed by measuring time to extrusion of a single glass bead. (2 mm) inserted 2 cm into the distal colon of the mice following fasting the animals for 12 h. Fecal output was assessed by measuring the total number and total weight of fecal pellets the animals produced in a 60 min period. A baseline measure was taken 2 days prior to MPTP treatment and then weekly following treatment for 4 weeks. MPTP-treated mice demonstrated reduced colon motility 3 and 4 weeks following treatment with the size of the effect increasing each week following treatment. No difference was found between the groups when fecal output was measured. TH levels were reduced by roughly 50% in the MPTP treated group. These findings demonstrated that MPTP-treated mice have a modest constipation effect relative to non-treated animals. Further work increasing the MPTP exposure and/or the duration to measure following constipation following treatment may increase the dynamic range of the model.

Disclosures: R.O. Pussinen: None. **A.J. Nurmi:** None. **R. Hodgson:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

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Topic: C.03. Parkinson’s Disease

Support: NAT-VIEP-BUAP 2016-2017

Title: Activation of the CB1 receptor in the Globus Pallidus externus modulates the fine motor skills of hemiparkinsonian rats

Authors: *I. LIMON PEREZ DE LEON, A. PATRICIO-MARTÍNEZ, A. S. BÁEZ-CORDERO
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Abstract: The afferent and efferent pathways of globus pallidus externus (GPe) participate in different functions and dysfunctions in the processing of the information of the basal ganglia (BG), and coordinate the neuronal activity in the BG. Cannabinoid Receptor 1 (CB1R) is abundantly expressed in the BG and plays an important role in the modulation of motor activity. Pharmacological antagonism of the CB1R decreases the motor asymmetry of hemiparkinsonian rats. The aim of this study was evaluated the fine motor skills of hemiparkinsonian rats after the activation of CB1 receptor in GPe. Male Wistar rats (270-300g) were trained on the staircase test for ten days. Subsequently, the rats received unilateral 6-OHDA injection into the medial forebrain bundle by stereotaxic surgery. Fourteen days post-surgery, animals were evaluated with the turning behavior test induced by Apomorphine (0.5mg/kg s.c.). Only rats that recorded 6 turns per minute were cannulated in the GPe at 22 day post-surgery. At 17 day post-surgery rats were evaluate in staircase test, we quantified the number of pellets eaten. The results indicate that the 6-OHDA group decrease number of pellets eaten, respect to the control group. At 25 day post-surgery, the rats received either 1µL de ACEA [1µM] (agonist CB1R), 1µL de AM251 [10µM] (antagonist CB1R), ACEA+AM251, or DMSO 0.01% for six days at the GPe. We found that the activation and inhibition of CB1R don’t cause a beneficial effect on the fine motor skills, respect to 6-OHDA+DMSO group. Interestingly the group that received both drugs decrease the number of pellets eaten in compare with control group. When evaluated the CB1R expression, we observe that in the 6-OHDA group decrease the expression in the ipsilateral GPe, while that in the group with AM251 recover the CB1R expression. In conclusion the CB1R activation in the denervated GPe avoids the fine motor skills impairment progression in a PD rat model; however further studies are necessary to elucidate the role of CB1R on fine motor skills.

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Poster

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Title: Sirtuins expression and olfactory dysfunction after NMDA-induced olfactory bulb excitotoxicty

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Abstract: Excitotoxicity is a key factor in neurodegenerative disorders such as Parkinson’s disease, in which olfactory dysfunction is an early symptom. However, the role of excitotoxicity and the underlying mechanisms involved in the olfactory dysfunction occurring in this disorder are still unknown. In addition, during excitotoxicity, a depletion of cellular nicotinamide adenine dinucleotide (NAD+), an important energy substrate, occurs leading to cell death. Sirtuins (SIRTs1-7) are a family of NAD+-dependent protein deacetylases believed to play an important role in cellular stress resistance and neuroprotection. Although SIRTs expression has been reported in the olfactory bulb (OB), their role in the excitotoxicity-induced olfactory dysfunction is still unknown.
We investigated the olfactory dysfunction and the changes in SIRTs and neurogenesis markers expression induced by the bilateral administration of the glutamate agonist N-methyl-D-aspartate (NMDA) in the OBs.
Rats were maintained in a food-deprivation schedule. Olfactory discrimination tests were performed before, 1 and 2 weeks after NMDA-lesion. NMDA (3 injections of 1.5 µl of a 12 mg/ml solution) or vehicle was bilaterally injected into OBs. Nissl staining, NeuN, SIRT-1, SIRT2, and SIRT-4 immunohistochemistry were performed in OB. Polysialylated-neural cell adhesion molecules (PSA-NCAM), and Ki67 immunohistochemistry were performed in the subventricular zone.
NMDA induced neural injury through all bulb layers. One week after NMDA lesions, animals showed a 70% decrease in correct olfactory trials ($p<0.01$) and an increase on the time spent to achieve correct odour ($p<0.05$). A recovery of olfactory function ($p<0.01$) associated to an increase in OB SIRT-1 and SIRT-4 ($p<0.01$) and in neurogenesis markers ($p<0.01$) expressions were observed two weeks after lesion.
The present results suggest that the increase in OB SIRT-1 and SIRT-4 expression may be involved in the repair mechanisms underlying the recovery of excitotoxicity-induced olfactory

dysfunction.
This study was sponsored by a grant from Fundació La Marató TV3 (110610)

Disclosures: C.A. Marin: None. **M. Bonastre:** None. **C. Langdon:** None. **B. Callejas:** None. **I. Alobid:** None. **J. Mullol:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.28/W22

Topic: C.03. Parkinson’s Disease

Support: CNPq - Brazil

CAPES - Brazil

Title: Ultrastructural and neurochemical changes in a model of Parkinsonism induced by Reserpine

Authors: P. C. LEAL[1], J. M. BISPO[2], L. C. R. F. LINS[2], M. F. SOUZA[2], C. MOORE[5], M. MARCHIORO[2], A. M. RIBEIRO[6], R. H. SILVA[7], A. M. GOIS[3], *M. A. FREIRE[8], C. K. MESHUL[5,9], J. SANTOS[4]
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Abstract: Parkinson’s disease is mostly know as a dopamine deficiency syndrome; however, studies have considered this pathology as a multi-systemic disease in which the neurodegenerative process extends beyond the dopaminergic system (Politis & Niccolini, 2014). Aim: The purpose of the present study was to investigate a possible relationship between dopamine levels and serotonergic system changes as well as the ultrastructural modifications of these neurons in premotor phase of a model of parkinsonism induced by low dose of reserpine. Methods: 22 seven-month- old male Wistar rats were used. All procedures were approved by the local ethics committee (protocol number 33/2016). The rats were randomly allocated to one of two groups: control (CTL: n = 11) or reserpine-treated (RES: n = 11). The animals received 4 subcutaneous injections of vehicle (CTL) or 0.1 mg/kg of reserpine (RES) at a volume of 1 ml/kg body weight, every other day. The animals were then euthanized 48h after the 4th injection for immunohistochemical (TH, 5-HT) and ultrastructural analysis in the following

areas: hippocampus proper (CA1 and CA3 sub regions), dentate gyrus (DG) and medial prefrontal cortex (mPFC). Results: Serotonin or TH levels were assessed by analysis of relative optical density (ROD). Student's *t* test revealed significant difference between groups (CTL, RES) with 5-HT level decreased in RES group in CA1 [t (20) = 2.77, p = 0.01], CA3 [t (20) = 2.13, p = 0.04] and mPFC [t (19) = 5.17, p < 0.0001]. Regarding TH levels, Student's *t* test revealed significant difference between groups only in CA1 [t (20) = 2.34, p = 0.02] with TH level decreased in RES group. Moreover, an increase in the area (μm^2) of 5HT labeled ultrastructure (axon terminal) was observed in RES group in CA1 (p = 0.001) and mPFC (p = 0.032). Conclusion: The evidence of alterations in 5-HT levels in premotor phase of PD highlights the importance of looking beyond the nigrostriatal system to elucidate the underling mechanisms and deficits in other neurotransmitters system. Additionally, the low-dose reserpine treatment has an early effect on axonal ultrastructure and as the axonopathy in PD has been increasingly recognized, the focus on axonal neurobiology is noteworthy for both neuroprotective and restorative therapeutics, and the progressive reserpine rat model can be a useful tool in this search.

Disclosures: P.C. Leal: None. **J.M. Bispo:** None. **L.C.R.F. Lins:** None. **M.F. Souza:** None. **C. Moore:** None. **M. Marchioro:** None. **A.M. Ribeiro:** None. **R.H. Silva:** None. **A.M. Gois:** None. **M.A. Freire:** None. **C.K. Meshul:** None. **J. Santos:** None.

Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 133.29/W23

Topic: C.03. Parkinson's Disease

Support: Brain Canada

Krembil Foundation

Parkinson Canada

Title: Increasing axonal arborization size of dopamine neurons to produce a better mouse model of Parkinson's Disease

Authors: *P. CASSIDY, N. BÉLANGER, W. TANGUAY, L.-É. TRUDEAU
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Abstract: INTRODUCTION: In Parkinson's disease (PD), dopamine (DA) neurons of the *substantia nigra pars compacta* (SNc) are a key subset of neurons particularly vulnerable to degeneration. Recent work in our laboratory showed that in cultured DA neurons, energetic metabolism, levels of oxidative stress, and vulnerability to toxins are a function of axonal

arborization size (Pacelli et al., 2015). It has been theorized that the arborization size of a single DA neuron in humans is much larger than in rodents, which could account in part for the apparently higher resilience of rodent DA neurons. **HYPOTHESIS:** Partial lesions of SNc DA neurons in rats have been shown to induce compensatory axonal sprouting in surviving neurons. Our hypothesis is that a partial lesion in the neonate mouse SNc will lead to residual DA neurons in the adult mouse that have a much larger axonal arborization, elevated energetic needs, and increased basal vulnerability. This compensating DA neuron population would thus be predicted to exhibit increased vulnerability to cellular stress and would potentially undergo age-dependent PD-like neurodegeneration. **RESULTS:** We induced a lesion of approximately 50% of SNc DA neurons by a unilateral injection of the neurotoxin 6-hydroxydopamine (6-OHDA) in neonatal (P5) transgenic DAT::IRES-Cre mice. These mice were then evaluated at 3 months of age. In a first step, we quantified the axonal arborization size of surviving DA neurons by infecting a sub-population of these neurons via intranigral injection with a virus allowing conditional expression of green fluorescent protein (GFP). Lesion-induced changes in behavior were also evaluated. We identified a dose of 6-OHDA inducing an approximate 50% lesion of SNc DA neurons in neonates. Behavior testing has revealed significant differences in rotarod performance, apomorphine-induced rotations, and actimetry measures when comparing groups of lesioned and sham mice. Compensatory axonal sprouting was confirmed in surviving SNc and VTA DA neurons. In a second step, we now plan to examine the vulnerability of compensating DA neurons at adult ages in response to intra-nigral infection with a virus overexpressing WT human alpha-synuclein. This paradigm has the potential to better model in the mouse the high basal vulnerability of DA neurons in Parkinson’s disease.

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Poster

133. Parkinson's Disease: Rodent Toxin and Behavior Models

Location: Halls A-C

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Program#/Poster#: 133.30/W24

Topic: C.03. Parkinson’s Disease

Support: VA Merit Review (BX000552-06)

Title: Exercise in an animal model of Parkinson's disease: motor recovery but not disease modification

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Abstract: Many clinical studies have reported on the benefits of exercise therapy in patients with Parkinson's disease (PD). However, it has been shown that exercise cannot stop the progression of PD or facilitate the recovery of dopamine (DA) neurons in the substantia nigra (SN) (Bega et al 2014). To tease apart this paradox, we utilized a progressive MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetra-hydropyridine) mouse model in which we initiated 4 weeks of treadmill exercise after the completion of toxin administration (i.e., restoration)(Goldberg et al., 2011). We found in our MPTP/ exercise (MPTP+EX) group several measures of gait function that recovered compared to the MPTP only group, including stride swing time and hindpaw stride length. Interestingly, analysis of nigrostriatal tyrosine hydroxylase (TH) showed a slight recovery in the MPTP+EX compared to the MPTP only groups, however this increase was not statistically significant compared to the MPTP only groups. Using 3 different methods to quantify the number of TH+ neurons in the substantia nigra pars compacta (SNpc), including stereology, cell surface counts and the average number of TH+ cells/section, the results were nearly identical, showing a small but non-statistical increase in TH+ cells in the MPTP+EX compared to either of the MPTP only groups. This increase was still statistically significant compared to the vehicle (VEH) group. TH-/cresyl violet stained cells were increased in all of the MPTP groups, including the MPTP+EX compared to the VEH groups, showing there was an increase in cells not expressing TH. These small increases in TH+ terminals/cells could not account for the full recovery of motor function in the MPTP+EX animals. Mice treated with four weeks of MPTP had a statistically significant 170% increase in the ratio of glycosylated/non-glycosylated dopamine transporter (DAT), and a 200% increase in IBA-1 levels (a general marker for microglia) in the striatum. The MPTP+EX group showed a near full recovery of these markers back to the VEH levels. Consistent with what others have shown, there is an increase in GLT-1 levels in the striatum due to exercise but there was no change in the MPTP only groups. There was also no change in striatal BDNF protein expression between any of the treatment groups. Our data suggests that motor recovery was not prompted by any significant restoration of DA neurons or terminals, but rather the recovery of the DA transporter and dampening the inflammatory response. Although exercise does not promote recovery of nigrostriatal DA, it could still be used as supplemental therapy in conjunction with pharmaceutical methods for controlling PD symptoms.

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Poster

134. Dystonia

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Topic: C.04. Movement Disorders

Support: NIH Grant NS54246

NIH Grant NS72872

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NIH Grant NS82244

Tyler's Hope for a Dystonia Cure, Inc.

Bachmann-Strauss Dystonia and Parkinson Foundaiton

Title: Improved survival and lack of overt dystonia in torsinA conditional knockout mice

Authors: *Y. LI, F. YOKOI, F. JIANG, K. DEXTER, B. SALVATO
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Abstract: DYT1 early-onset generalized dystonia is a movement disorder characterized by abnormal torsion posture and repeated movement. DYT1 dystonia is caused by heterozygous mutations in *DYT1/TOR1A*, coding for torsinA. Most patients have a heterozygous mutation of an in-frame trinucleotide deletion (ΔGAG), corresponding to a glutamic acid loss in the C-terminal region of torsinA. Heterozygous *Dyt1/Tor1a* ΔGAG knock-in (KI) mice, which has the corresponding trinucleotides deletion in the endogenous *Dyt1/Tor1a* gene, exhibit long-term depression (LTD) deficits of the cortico-striatal pathway, sustained contraction and co-contraction of agonist and antagonist muscles, and motor deficits. These phenotypes are ameliorated by trihexyphenidyl, which is commonly used for dystonia patients. Both heterozygous *Dyt1* KO mice and *Dyt1* knock-down mice also show similar motor deficits, suggesting that a partial loss of torsinA function may contribute to the motor deficits. Contrast to the heterozygous mouse models, homozygous *Dyt1* KI and KO mice die at neonatal period. A recent study shows weak walking, abnormal twisting and lethality within postnatal 16 days (P16) in an N-CKO mouse model, which has a heterozygous *Tor1a* /*Dyt1* knockout (KO) in one allele and *Nestin-cre*-derived conditional KO in another allele. It also exhibits severe growth retardation, which is not common in DYT1 dystonia patients. We generated N-CKO using a different line of *Tor1a/Dyt1* loxP mice generated previously in the lab. Instead of complete lethality before P16, majority of the N-CKO mice could grow up to adult and did not show overt twisting or dystonic movements. The adult N-CKO mice showed mild growth retardation and motor deficits as detected in wire suspension test. Further histochemical experiments will be performed to determine whether there is increased neurodegeneration in the N-CKO mice.

Disclosures: Y. Li: None. **F. Yokoi:** None. **F. Jiang:** None. **K. Dexter:** None. **B. Salvato:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.02/W26

Topic: C.04. Movement Disorders

Support: 1R01NS077730-01A1

Title: TorsinA loss of function causes perinuclear proteostatic abnormalities and nuclear pore complex defects

Authors: *S. S. PAPPAS, C.-C. LIANG, C. O. RIVERA, W. T. DAUER
Dept Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Accumulation of ubiquitin in the nuclear envelope of neurons lacking the DYT1 dystonia-related protein torsinA is believed to occur in a select group of cells. This phenomenon is thought to contribute to the degeneration of these discrete cell types. In contrast to this view, we demonstrate that perinuclear ubiquitin accumulation is a widespread and developmentally regulated phenomenon that is present in nearly all torsinA null neurons, including those not susceptible to cell death. Affected neurons also display altered morphology of the nuclear lamina and severe disruption in nuclear pore localization. Strikingly, the accumulated ubiquitin resolves by one month of age, but the nuclear pore complex abnormalities persist for up to seven months of age. These results further link nuclear pore abnormalities with torsinA loss of function and implicate altered nucleocytoplasmic trafficking in the pathogenesis of DYT1 dystonia.

Disclosures: S.S. Pappas: None. **C. Liang:** None. **C.O. Rivera:** None. **W.T. Dauer:** None.

Poster

134. Dystonia

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Topic: C.04. Movement Disorders

Support: NIH Grant P50NS037409

NIH Grant P01NS087997

Title: Common physiological and neurochemical alterations of striatal cholinergic function in DYT-TOR1A and DYT-THAP1 knock-in mouse models of dystonia

Authors: *K. L. ESKOW JAUNARAJS[1], M. SCARDUZIO[1], M. E. EHRLICH[3], L. MCMAHON[2], D. STANDAERT[1]
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Abstract: Dystonia is a movement disorder, which typically results in twisted postures due to abnormal muscle contraction. Clinical and experimental data point to abnormalities of striatal cholinergic function in dystonia. Two of the most common genetic forms of isolated dystonia are those resulting from mutations in the TOR1A (DYT-TOR1A) and THAP1 genes (DYT-THAP1). Knock-in (KI) mouse models for mutations underlying both DYT-TOR1A and DYT-THAP1 have been developed. We hypothesize that physiological and neurochemical alterations of striatal cholinergic interneurons may be a shared mechanism of isolated dystonias. To test this idea, we used heterozygous KI mice with the disease-causing ΔGAG mutation of the gene encoding TorsinA and with the disease-causing C54Y mutation of the gene encoding THAP1, as well as their wild-type controls. *In vivo* reverse microdialysis was employed to determine striatal acetylcholine efflux and *ex vivo* slice cell-attached electrophysiological recordings were used to examine the pacemaking activity of cholinergic interneurons. In particular, we sought to determine whether cholinergic interneurons from DYT-THAP1 KI mice displayed “paradoxical excitation” in response to the dopamine D2 receptor agonist, quinpirole, an endophenotype observed across multiple rodent models of DYT-TOR1A and proven to be a consequence of heightened cholinergic tone. Results showed that both DYT-TOR1A and DYT-THAP1 mice had elevated acetylcholine in the striatum both in the basal state and in the presence of neostigmine. Furthermore, both models also displayed dopamine D2 receptor-induced “paradoxical excitation” in the firing rate of striatal cholinergic interneurons. These data suggest that DYT-TOR1A and DYT-THAP1 have common pathophysiological and neurochemical physiology and that striatal cholinergic dysfunction may underlie both of these forms of dystonia. Further investigation of other mouse models of dystonia may further extend this common theme of striatal cholinergic dysfunction as a mechanism of dystonia.
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Poster

134. Dystonia

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Topic: C.04. Movement Disorders

Support: Tyler's Hope

R01 NS075012

R01 NS058487

R01 NS082244

R01 NS077730

T32 NS082168

University of Florida McKnight Brain Institute pilot imaging grant

Title: Forebrain knock-out of torsinA reduces striatal free-water and impairs whole-brain connectivity in a symptomatic mouse model of DYT1 dystonia

Authors: *J. C. DESIMONE[1], S. S. PAPPAS[5], M. FEBO[2], R. G. BURCIU[1], P. SHUKLA[1], L. M. COLON-PEREZ[3], W. T. DAUER[6], D. E. VAILLANCOURT[4]
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Abstract: Early-onset generalized (DYT1) dystonia is characterized by repetitive muscular co-contractions and disabling postures that manifest due to loss-of-function in the protein torsinA. Dysfunction of the striatum has been implicated in DYT1 pathogenesis. However, the degree to which aberrant striatal pathology influences connected motor circuitry remains unknown. To examine this issue, we conditionally deleted torsinA from forebrain cholinergic and GABA-ergic precursors, which creates a symptomatic dystonia mouse model and selective degeneration of dorsal striatal cholinergic interneurons. We performed diffusion MRI and resting-state functional MRI on conditional knock-out (cKO) mice to define abnormalities of diffusivity and functional connectivity in cortical, subcortical, and cerebellar networks. The striatum was the only region to exhibit an abnormality of diffusivity, reflecting structural adaptations to striatal cholinergic interneurons. The striatum of cKO mice exhibited widespread and striking increases in functional connectivity with somatosensory cortex, thalamus, vermis, cerebellar cortex and nuclei, and brainstem. The increased FC of striatum with multiple hindbrain regions in which torsinA function is preserved demonstrates that a genetically mutant structure can engage genetically normal structures in abnormal network-level connectivity. These findings have important implications for the assignment of a “causative” region in CNS disease, and demonstrate that an initial forebrain abnormality can coopt genetically normal hindbrain structures into a large-scale aberrant connectivity network.

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Poster

134. Dystonia

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Support: US Department of Defense Grant W81XWH-14-1-0282

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Stanley Fahn Award of the Dystonia Medical Research Foundation

Grant for International Mobility of the University of Malaga

Title: Exploring the interaction between eIF2α dysregulation, acute endoplasmic reticulum stress and DYT1 dystonia

Authors: *G. BEAUVAIS[1], N. RODRIGUEZ-LOSADA[2], L. YING[1], Z. ZAKIROVA,[3], J. L. WATSON[1], B. READHEAD[3], P. GADUE[1], D. L. FRENCH[1], M. E. EHRLICH[3], P. GONZALEZ-ALEGRE[1]
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Abstract: Abstract
DYT1 dystonia is a neurological disease caused by dominant mutations in the *TOR1A* gene, encoding for the endoplasmic reticulum (ER)-resident protein torsinA. Recent reports linked expression of the DYT1-causing protein with dysregulation of eIF2α, a key component of the cellular response to ER stress. We hypothesized that torsinA is involved in the neuronal response to acute ER stress and expression of its mutant form would alter this process *in vivo*. To test this hypothesis, we measured responses to ER stress triggered by tunicamycin or d-amphetamine in induced pluripotent stem cell-derived striatal neurons, DYT1 *knockin* mice and DYT1 transgenic rats. In addition, we completed an unbiased RNA-Seq-based transcriptomic analysis of embryonic brain tissue in heterozygous and homozygous DYT1 *knockin* mice. We found that torsinA undergoes early upregulation upon the induction of ER stress. Moreover, our findings support a dose-dependent effect of mutant torsinA expression on eIF2α dysregulation in striatum and cerebellum of DYT1 mice and rats. Finally, increased basal phosphorylation of eIF2α in DYT1 transgenic rats is associated with an abnormal response to ER stress. In sum, these findings support previous reports linking torsinA function, eIF2α signaling and the neuronal response to ER stress *in vivo*. Furthermore, we also describe novel protocols to investigate neuronal ER stress in cultured neurons and *in vivo*.

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Poster

134. Dystonia

Location: Halls A-C

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Program#/Poster#: 134.06/W30

Topic: C.04. Movement Disorders

Title: Serotonin mediates stress induced dystonia through 5HT2A receptor in tottering mice

Authors: *J. KIM[1], S. CHAE[2], S. KIM[3], G. PARK[2], D. KIM[1]
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Abstract: Dystonia is the third most common movement disorder after essential tremor and Parkinson's disease. Stress increases muscle tension and the risk of dystonia, a co-contraction of agonist and antagonist muscles, which significantly interfere with motor performance. Here, we reveal the serotonergic mechanism for the stress-induced muscle tension in a genetic mouse model of dystonia (CACNA1A$^{tot/tot}$). When CACNA1A$^{tot/tot}$ mice were placed in novel place, they developed dystonia with increased neuronal excitability. When administered selective 5HT-2A receptor antagonist, MDL100907, tottering mice show no stress-induced dystonia with decreased neuronal excitability but other serotonergic blockers for 5HT-1A or 5HT-3 led no significant effects in dystonia level. These results suggest that serotonin plays important role in the generation of stress-induced dystonia through 5HT-2A receptors and this gives insights on pharmacological relieve of motor dysfunction in dystonia patients.

Disclosures: **J. Kim:** 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.; KAIST. **S. Chae:** None. **S. Kim:** None. **G. Park:** None. **D. Kim:** None.

Poster

134. Dystonia

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Topic: C.04. Movement Disorders

Support: Wellcome Trust Strategic Award in Synaptopathies

Title: Do dystonia mutations in hippocalcin change the slow afterhyperpolarization?

Authors: *C. L. DIXON, D. M. KULLMANN
DCEE, Univ. Col. London, London, United Kingdom

Abstract: Hippocalcin (HPCA) is a small, myrostylated cytosolic protein. With increased calcium, HPCA translocates to membrane compartments, interacting with diverse binding partners. In some neurons it causes a slow afterhyperpolarisation (sAHP). Mutations in HPCA cause dystonia by an unknown mechanism.
The mutations T71N and N75K are in a calcium binding domain, so we tested whether calcium-evoked translocation was impaired. We transduced primary hippocampal neuron cultures with HPCA-RFP for live cell imaging. Upon addition of ionomycin, both mutants and wild-type HPCA translocated to membrane domains. Compartmentalisation (as measured by maximum standard deviation of fluorescence) was 140 ± 27 % of wild-type for T71N, and 68 ± 18 % of wild-type for N75K (mean ± SEM, $n \geq 6$ wells each, $p > 0.05$).
Lacking clear evidence for a calcium binding deficit in the mutants, we used voltage clamp electrophysiology to test whether the mutants produced a sAHP current. For cultured hippocampal neurons transduced with wild-type HPCA-RFP, I_{sAHP} amplitude was 58 ± 13 pA. For T71N it was 40 ± 4 pA and for N75K 24 ± 7 pA ($n \geq 6$ cells each, $p < 0.05$ for N75K). These data support changes in the sAHP as a plausible mechanism for dystonia associated with HPCA mutations.

Disclosures: C.L. Dixon: None. **D.M. Kullmann:** None.

Poster

134. Dystonia

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Support: Grant NASU (# II - 1- 12) to PB

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Osteopathic Heritage Research Foundation to VV

Title: Perturbed Ca^{2+}-dependent signaling of DYT2 hippocalcin mutants as mechanism of autosomal recessive dystonia

Authors: *N. I. KONONENKO[1], D. S. OSIPENKO[1], A. V. DOVGAN[1], O. A. RYBACHUK[1], J. ZHANG[2], V. VENKATARAMAN[2], P. BELAN[1]
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Abstract: Dystonia is a common movement disorder characterized by twisting or repetitive movements with or without tremor. Recent research has demonstrated that autosomal recessive form of primary isolated dystonia (DYT2) is developed due to the point mutations in the neuronal Ca^{2+} sensor (NCS) protein, hippocalcin (HPCA). HPCA translocation upon Ca2+-dependent conformation modification (Ca^{2+}-myristoyl switch) from the cytosol to plasma membrane controls many neuronal mechanisms including slow afterhyperpolarization (sAHP) that strongly contribute to modulation of neuronal activity and may potentially underlie DYT2. Two HPCA mutations, associated with DYT2, are located in Ca^{2+}-binding domain, EF-hand 2, suggesting perturbed Ca^{2+}-dependent signaling and sAHP in these mutants compared to wild-type HPCA. To test this hypothesis, at first, we studied biophysical properties and Ca^{2+} buffering capacity of HPCA and its T71N and N75K mutants tagged by different fluorescent proteins in HEK cells. Decay constants and amplitudes of mutants' translocation transients to the plasma membrane in response to Ca^{2+} uncaging were significantly changed compared to HPCA, in particular, demonstrating that N75K mutation leads to substantial decrease in both HPCA affinity to Ca^{2+} and Ca^{2+} buffer capacity while preserving Ca^{2+}-myristoyl switch. Then, in order to reveal functional consequences of HPCA mutant expression we studied Ca^{2+}-dependent translocation of HPCA and its mutants in cultured hippocampal neurons. Short bursts of action potentials and theta rhythms, inducing long-term modulation of synaptic plasticity, produced HPCA translocation to the plasma membrane while N75K mutant couldn't decode this type of neuronal activity by translocation. At the same time strong and prolonged neuronal stimulation led to the same spatio-temporal patterns of translocation having equal amplitudes that implies that Ca^{2+}-myristoyl switch remained intact. N75K overexpression in the hippocampal neurons did not significantly change sAHP induced by translocation of endogenous HPCA indicating that the mutant neither blocks nor increases sAHP. Thus, N75K HPCA can not induce sAHP that results in an increased neuronal excitability shown in simulation experiments. We conclude that N75K mutation found under DYT2 dystonia results in loss-of-function in HPCA Ca^{2+}-dependent signaling, increased neuronal excitability and abnormalities in patterns of neuronal activity. Altogether it may lead to the increased excitability of motor neurons in the spinal cord being a mechanism for the expression of movement disorders observed in this disease.

Disclosures: N.I. Kononenko: None. **D.S. Osipenko:** None. **A.V. Dovgan:** None. **O.A. Rybachuk:** None. **J. Zhang:** None. **V. Venkataraman:** None. **P. Belan:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.09/W33

Topic: C.04. Movement Disorders

Support: Center for Brain Repair

Bryan Jackson Research and Discovery Program

Title: Expression of the novel DYT5 peptide DRDp73 downregulates the dopamine biosynthesis pathway in neuroblastoma cells

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Abstract: GTP Cyclohydrolase 1 (GCH1) is a rate limiting catalyst of dopamine biosynthesis. Heterozygous mutations in the *GCH1* gene are associated with familial Dopa-Responsive Dystonia (DRD), also known as DTY5 dystonia. One such mutation is a single nucleotide polymorphism (SNP) that introduces an upstream open reading frame (uORF) in the 5' untranslated region of *GCH1*. The uORF serves as a translational repressor of the canonical ORF. Studies in HEK293 cells co-transfected with wild type GCH1 and SNP-GCH1 constructs show that translation of the uORF generates a novel, 73 a.a. peptide, DRDp73, and reduces GCH1 expression. Moreover, DRDp73 localizes in the nucleus of the transfected HEK293T cells, whereas GCH1 is found in the cytoplasm. Since the HEK293 cells do not express GCH1 or the dopamine biosynthetic pathway, in the present study, we transfected the neuroblastoma cell line SK-N-Be(2)-M17 (BEM) with the SNP-GCH1 construct. The BEM cells express the dopamine biosynthesis pathway permitting evaluation of the effects of the SNP on the expression of GCH1 and other key intermediates in dopamine biosynthesis. We found that there was a significant decrease in the expression of GCH1, BH4 and tyrosine hydroxylase, key regulators of dopamine biosynthesis, in the BEM cells transfected with the SNP-GCH1 construct. Currently, we are extending the studies in primary cultures of embryonic mouse ventral midbrain neurons and lymphoblastoid cells derived from DYT5 patients.

Disclosures: L. Jones: None. **I.A. Armata:** None. **D.M. Mc Carthy:** None. **N. Sharma:** None. **P.G. Bhide:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.10/W34

Topic: C.04. Movement Disorders

Title: Impairment of neuronal differentiation of human induced neural stem cells by TOR1A overexpression

Authors: *P. CAPETIAN[1,2], F. STENGEL[2], F. VULINOVIC[2], C. KLEIN[2]
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Abstract: Background:
Autosomal dominant inherited, early-onset torsion dystonia (DYT-TOR1A) is known as the most common mutation in inherited dystonia. It is caused by a three nucleotide (GAG) deletion (ΔE) in the *TOR1A* gene. *TOR1A* encodes for TorsinA an AAA+ chaperone protein, which is localized in the endoplasmic reticulum. In contrast to TOR1A wildtype (wt), the ΔE mutation shows a perinuclear localization when overexpressed. Yet, no human neuronal in-vitro cell model of this mutation has been generated.
Objectives:
Exploring the effects of TOR1A-wt and TOR1A-ΔE during differentiation and maturation in a human neuronal in-vitro cell model
Methods:
For our study, we employed directly reprogrammed induced neural stem cells (iNSC) from human fibroblasts of healthy volunteers. We used lentiviral transduction of a tet-ON system to induce overexpression of MYC-tagged TOR1A-wt and TOR1A-ΔE in three control lines by addition of doxycycline. Cells were differentiated to mature neurons by addition of the NOTCH-inhibitor DAPT. We determined TOR1A expression by western blotting and by immunofluorescence of the MYC-tag in colocalization with nestin and MAP2. We examined the influence of TOR1A on proliferating neural stem cells, neuronal differentiation and mature neurons.
Results:
Cell lines showed a robust and inducible overexpression of MYC-tagged TOR1A after transduction and selection. As anticipated from animal overexpression models, the wildtype form was present throughout the entire endoplasmatic reticulum, while the mutant form aggregated in the perinuclear membrane. Overexpression of neither TOR1A-wt nor TOR1A-ΔE had an impact on the cell number of nestin-positive neural stem cells, nor mature MAP2-positive neurons. However. The overexpression of both variants during differentiation led to a highly significant reduction of mature neurons after 30 days in a dose dependent manner.
Conclusion:
Overexpression of TOR1A in its wildtype or mutant form had no negative effect on the viability of neural stem cells or mature neurons. However, neuronal differentiation displayed a particular susceptibility to the altered expression levels of TOR1A regardless of the respective variant. This effect has not yet been demonstrated in animal overexpression models and might represent a specific vulnerability of the developing human cns. Therefore, our data emphasizes the importance of human neural cell models in neuroscientific research.

Disclosures: P. Capetian: None. **F. Stengel:** None. **F. Vulinovic:** None. **C. Klein:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.11/W35

Topic: C.04. Movement Disorders

Support: Schmitt Program on Integrative Brain Research GR503091

Geoffrey Waasdrop Child Neurology Fund

Wilbur Smith Endowment

Title: Quantitative measurements of deficit type and severity in focal emouchure dystonia

Authors: *A. E. MORRIS[1], S. A. NORRIS[2], A. Z. SNYDER[2], J. S. PERLMUTTER[2], J. W. MINK[1]
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Abstract: FED is a focal task-specific dystonia that impairs orofacial motor control in wind musicians. It has an estimated 1% prevalence in brass musicians and causes professional disability. Little is known about mechanisms of FED, in part because there are few quantitative measures. We used acoustic methods to quantify specific features of FED and develop an instrument to assess its overall severity.
Adult brass musicians with and without FED were studied while playing sustained tones and sequences. Sound recordings were analyzed in amplitude, frequency, and time domains using MATLAB. Pitch inaccuracy, instability (jitter and shimmer), sound breaks, and timing variability (inter-onset interval coefficient of variation, IOI CoV) were quantified for each note. Tremor was assessed using fast Fourier transform (FFT) and short-time Fourier Transform (STFT). Non-rhythmic low-frequency variability was measured as power spectral density (PSD) in the 3-8 Hz band. Acoustic variables were Z-score normalized across subjects and averaged to obtain a COmposite BRass Acoustic Severity (COBRAS) score that was compared with the clinical global impression (CGI) of severity assessed by two movement disorders neurologists. We recruited 9 brass musicians with FED and 6 brass musician controls (CTL). FED had higher pitch inaccuracy (*Mdn* = 100%) than CTL (*Mdn* = 62%) subjects, U = 8, p = 0.03. Shimmer was greater in FED (*Mdn* = 3.0%) than CTL (*Mdn* = 2.0%) groups, U = 9, p = 0.04. Jitter had a similar trend (*Mdn* FED = 0.6%, CTL = 0.4%) but was not significance, U = 14, p = 0.14. Breaks were far more frequent in FED (*Mdn* = 0.34%) than CTL musicians (*Mdn* = 0.05%), U = 0, p < 0.001. There was no difference in rhythmic variability (IOI CoV) in FED (*Mdn* = 0.08) and CTL (*Mdn* = 0.06) groups, U = 13, p = 0.1. Tremor in FED was 4-6 Hz and often intermittent. Additional low-frequency instability led to an increased 3-8 Hz PSD in musicians with FED

(*Mdn* = 0.006) versus CTL (*Mdn* = 0.001), U = 2, p < 0.01. Detectable tremor was not present in any controls. Subjects with FED differed in their patterns of impairment across variables. COBRAS scores were significantly higher in the FED (*Mdn* = 0) compared with CTL (*Mdn* = -0.6) groups, U = 7, p = 0.02, and highly correlated with CGI in musicians with FED, Spearman *r* = 0.94, *p* < 0.001.
Acoustic variables distinguish musicians with FED from those without and can be used to measure severity. The relative contribution of each variable to global severity differed between subjects, but COBRAS scores correlated highly with CGI. These quantitative measures can be used to assess response to treatment and to measure severity in research. Our results also provide a foundation to develop a clinical rating scale for FED.

Disclosures: A.E. Morris: None. **S.A. Norris:** None. **A.Z. Snyder:** None. **J.S. Perlmutter:** None. **J.W. Mink:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.12/W36

Topic: C.04. Movement Disorders

Support: Collaborative Center For X-Linked Dystonia-Parkinsonism

Title: Assessing epigenetic marks in X-linked Dystonia-Parkinsonism

Authors: *A. DIOS[1], K. MUELLER[2], C. VAINE[2], K. MANGKALAPHIBAN[2], K. GLAJCH[2], N. SHARMA[2], L. OZELIUS[2], D. C. BRAGG[2], G. SADRI-VAKILI[2]
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Abstract: X-linked Dystonia-Parkinsonism (XDP) is a movement disorder that is endemic to the region of Panay, Philippines. Individuals with XDP have features of both dystonia and Parkinson's disease. All XDP patients have a haplotype consisting of 7 disease specific variants including a disease specific SVA-type retrotransposon insertion, a 48-bp deletion, and 5 single-nucleotide changes (DSC1, DSC2, DSC3, DSC10, and DSC12) which are mainly localized within the TAF-1 gene. TAF-1, a gene that encodes the TATA-Binding Protein (TBP) Associated Factor-1, is the largest component of a multi-subunit TFIID complex involved in RNA polymerase II mediated transcription. Recent findings suggest that there are differences in the transcription of exons flanking the SVA-type retrotransposon insertion site in the TAF-1 gene in fibroblasts and neuronal stem cells derived from XDP patients. Given that SVA-type insertions are associated with epigenetic modifications such as increases in DNA methylation, we sought to determine whether changes in transcription were due to changes in epigenetic marks. Using chromatin immunoprecipitation (ChIP) followed by RT-qPCR we assessed

whether there were changes in two epigenetic marks, DNA-methylation, a repressive epigenetic mark, and histone acetylation, a permissive epigenetic mark, along the TAF-1 gene, that may contribute to changes in TAF-1 gene expression in fibroblasts derived from individuals with XDP versus controls. DNA-methylation associated with intron 32, the region containing the disease specific SVA, or at DSC10 and DSC12 was not altered in XDP fibroblasts compared to control. Similarly, there was no significant change in global histone H3 or H4 acetylation in fibroblasts derived from XDP patients compared to familial matched controls. In addition, acetylated histone H3 occupancy at these regions or any other region across the TAF-1 gene was not altered in XDP patient fibroblasts compared to control. Our results demonstrate that DNA methylation or histone acetylation are not involved in regulating TAF-1 gene expression in fibroblasts derived from XDP patients, suggesting that alternative mechanisms of transcriptional regulation may be involved in XDP.

Disclosures: A. Dios: None. **K. Mueller:** None. **C. Vaine:** None. **K. Mangkalaphiban:** None. **K. Glajch:** None. **N. Sharma:** None. **L. Ozelius:** None. **D.C. Bragg:** None. **G. Sadri-Vakili:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.13/X1

Topic: C.04. Movement Disorders

Support: Crowley Carter Foundation

Lee/Ramo Chair in Health Technology

Title: Longterm multi-channel micro-electrode recording from basal ganglia and thalamus in children with acquired dystonia

Authors: *T. D. SANGER[1], M. LIKER[3], A. ROBISON[4], E. ARGUELLES[2], A. MASKOOKI[1]
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Abstract: The optimal target for deep brain stimulation (DBS) in children with acquired (secondary) dystonia is not known, and it is likely that the best target may vary depending on the etiology and anatomic distribution of injury in each child. We present 7 cases of a new technique for determining optimal neuro-anatomical targets. Up to 10 depth electrodes are implanted in each child in multiple brain regions, including subthalamic nucleus (STN), internal globus pallidus (GPi), and thalamic nuclei: ventral anterior (VA), ventrolateral anterior (VLa), ventral intermediate (Vim), and ventroposterolateral (VPL). Each electrode has 10 high-impedance

“micro” contacts capable of identifying single unit firing, and 6 “macro” contacts capable of identifying local field potentials and through which test stimulation can be performed. Awake children are monitored for 1 week in the epilepsy monitoring unit with continuous and simultaneous recording from all 160 contacts. Single-unit recording showed high firing rates that were poorly localized in GPi, and activity correlated with dystonic movement could be found in VL or Vim. When awake and at rest, most areas showed very low firing rates. Activity in Gpi and STN correlated most closely with contralateral dystonic EMG. Overflow was associated with activation in ipsilateral Vim as well GPi, consistent with a basal ganglia or thalamic origin of overflow. The optimal stimulation target varied between children, in some cases with rapid improvement of dystonic postures during stimulation in either VLa, Vim, or VPL. In agreement with the known clinical effect of pallidal stimulation, stimulation in GPi did not produce an effect during the recording period. Based on the recording and stimulation results, all of the children received up to 4 permanent stimulation leads connected to implanted pulse generators. Clinically optimal stimulation sites corresponded to regions in which activity correlated with dystonic EMG. In contrast with prior recordings in animals and adult humans, we found that activity is highly correlated with movement (voluntary or involuntary) and is very low at baseline. We found that patterns of activity associated with dystonic contractions differ between children. Since effective stimulation targets also differ, this likely reflects the varied neuroanatomic causes of this disorder and suggests that any computational model of dystonia must allow for multiple patterns of abnormal network activity.

Disclosures: **T.D. Sanger:** None. **M. Liker:** None. **A. Robison:** None. **E. Arguelles:** None. **A. Maskooki:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.14/X2

Topic: C.04. Movement Disorders

Support: NIH 5R01HD081346-03

Title: Simultaneous recordings from implanted electrodes in basal ganglia and thalamus in children with secondary dystonia

Authors: *E. ARGUELLES, A. MASKOOKI, M. ABOLFATH-BEYGI, D. FERMAN, T. SANGER
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Abstract: Dystonia is a movement disorder characterized by involuntary muscle contractions and abnormal postures. Dystonia has been associated with basal ganglia disfunction where

abnormal neural firing leads to aberrant plasticity, in which a complex set of physiological abnormalities leads to abnormal neural organization. Deep brain stimulation (DBS) of the internal segment of the globus pallidus is a common treatment for severe dystonia, however, the optimal DBS target in children with secondary dystonia is still unknown, and it is likely to change based on the etiology and anatomic distribution of injury in each child. We present data from 5 pediatric patients with secondary dystonia implanted with up to 10 depth electrodes (AD-TECH MM16C) in multiple brain regions, including subthalamic nucleus (STN), internal globus pallidus (GPi), ventrolateral nucleus of the thalamus (VL), ventral intermediate nucleus of the thalamus (VIM), and ventroposterolateral nucleus of the thalamus (VPL). Simultaneous single-unit recording form 10 high impedance micro-electrodes and local field potentials from 6 low impedance macro-electrodes were collected throughout one week, during which the patient stayed at the hospital's epilepsy monitory unit. These macro-electrodes were also used to test clinical stimulation. Our results did not show a consistent pattern of abnormality. Single-unit recording showed high firing rates that were poorly localized in GPi, and activity correlated with dystonic movement could be found in VL or VIM. In general, low firing rates were observed compared to prior recordings reported in animals and adult humans. This may reflect the fact that the recording electrodes were implanted under general anesthesia, thus, no active cells where used as reference to determine the electrode placement. In this case, our results may show an unbiased sample of basal ganglia and thalamic activity. Finally, the optimal stimulation target varied between children. Clinically, optimal stimulation sites corresponded to regions in which activity correlated with dystonic EMG.

Disclosures: E. Arguelles: None. **A. Maskooki:** None. **M. Abolfath-Beygi:** None. **D. Ferman:** None. **T. Sanger:** None.

Poster

134. Dystonia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 134.15/X3

Topic: C.04. Movement Disorders

Support: NIH Grant R01NS088160

Title: A functionally diverse network kernel shapes task specificity in focal dystonia

Authors: S. FUERTINGER[1], *K. SIMONYAN[2]
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Abstract: Task-specific focal dystonia (TSFD) is a movement disorder that selectively affects voluntary movements while performing learned and highly skilled motor tasks. Although its

clinical symptomatology is well described, the mechanisms underlying task specificity in dystonia is largely unknown. We examined resting-state functional connectomes of patients with different TSFD forms and compared them to healthy subjects to identify specific changes in brain networks, which may lead to manifestation of distinct forms of dystonia. For this, 16 patients (45.3±10.8 years; 8 females/8 males) with singer's laryngeal dystonia (SLD), spasmodic dysphonia (SD), writer's cramp (WC) and musician's focal hand dystonia (MFHD) were compared to 16 healthy professional musicians and non-musicians (43.9±11.9 years; 7 females/9 males). Next, to examine the influence of affected body region on functional network organization, we compared 16 patients with hand dystonia (MFHD+WC; 53.3±10.3 years; 8 females/8 males) to 16 patients with laryngeal dystonia (SLD+SD; 54.4±9.9 years; 8 females/8 males). By comparing 16 patients with musician's dystonia (SLD+MFHD; 52.2±9.8 years; 4 females/12 males) to 16 patients with non-musician's dystonia (SD+WC; 54.8±9.8 years; 5 females/11 males), we also analyzed the influence of the symptomatic task on resting-state connectome. Our analysis targeted group-specific functional network kernel, consisting of inter-modular hub relay regions that establish significantly higher connectivity across all subject network kernels than expected by chance. Abnormalities in primary sensorimotor cortex and thalamus were key findings when comparing TSFD to healthy controls. In addition, altered connectivity of the sensorimotor processing regions were specific for the kernel in laryngeal TSFD, while regions involved in motor control management were distinctly abnormal in hand TSFD. We further found that the functional network kernel of musician's TSFD included aberrant interactions between sensory and motor execution systems, while the kernel of non-musician's TSFD showed abnormal integration of sensory feedback for motor planning and cognitive processing. In this study, we introduce a novel concept of abnormal functional network kernel in dystonia, which carries specific characteristics of each TSFD form shaped by the interplay between affected body region and symptom manifestation. Our results permit new insights into the formation of large-scale functional specializations corresponding to task-specific brain network alterations in dystonia.

Disclosures: S. Fuertinger: None. **K. Simonyan:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.01/X4

Topic: C.05. Neuromuscular Diseases

Support: NIH/NINDS Grant NS095157-01(SV)

Title: Pre-symptomatic abnormalities and associated channelopathies in spindle afferent trigeminal mesencephalic V neurons in a SOD1G93A mouse model for amyotrophic lateral sclerosis

Authors: *S. SEKI[1], S. H. CHANDLER[1,2], R. MAHESHWARY[1], H. NISLY[1], A. P. SAMPATH[2,3], R. OLCESE[4], M. W. PAZOS[5], S. VENUGOPAL[1]
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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease wherein upper and lower motor neurons (MNs) progressively degenerate leading to muscle atrophy, paralysis and death. Recent evidence has suggested involvement of the fusimotor system in contributing to motor neuron vulnerability (Lalancette-Hebert et al., 2016, PNAS). Here we propose involvement of spindle afferent neurons in early disease development. In the present experiments, we used *in vitro* patch-clamp methods to record from primary sensory Mesencephalic V (Mes V) neurons that relay reflex and proprioceptive inputs from jaw muscle spindles to trigeminal MNs. We demonstrate early (P8-P14) abnormalities in membrane properties of these neurons in the well-characterized SOD1G93A mouse model (mSOD1) for ALS when there are no phenotypic behavioral deficits. Such neuronal changes included hypo-excitability and irregularity in spike discharge patterns of Mes V neurons displaying both burst and tonic discharge. Mean spike frequencies were significantly lower (WT burst: 61.77 Hz, n=11, mSOD1 burst: 45.77 Hz, n=16, p=0.014; WT tonic: 42.70 Hz, n=13, mSOD1 tonic: 32.20 Hz, n=8, p=0.046) and coefficient of variability was significantly higher (WT burst: 0.014, n=11, mSOD1 burst: 0.088, n=16, p=0.012; WT tonic: 0.026, n=13, mSOD1 tonic: 0.068, n=8, p=0.032) in mSOD1 animals. Such changes in discharge properties were absent in mutant visual sensory ganglion neurons although mutant SOD1 is ubiquitously expressed (WT: 11.6 Hz, n=11, mSOD1: 10.8 Hz, n=7, p>0.05). Further examination of ionic mechanisms mediating excitability changes in Mes V neurons using voltage-clamp experiments revealed reduction of persistent (WT: - 1.49 pA/pF, n=11, mSOD1: -0.98 pA/pF, n=12, p=0.034) and resurgent (WT: -6.34 pA/pF, n=11, mSOD1: -4.32 pA/pF, n=12, p=0.046) sodium currents and increase of 4-AP-sensitive slow potassium current (WT: 3.77 pA/pF, n=14, mSOD1: 8.40 pA/pF, n=4, p=0.021). Ongoing experiments are examining restoration of normal levels of sodium conductances using realistic computational models and dynamic-clamp technique to control membrane excitability and reverse abnormal excitability changes in mSOD1 Mes V neurons. For example, we are able to reverse irregular spike patterns in mSOD1 Mes V cells *in vitro* via injection of biophysically based resurgent sodium current. Together these experiments offer the first evidence of proprioceptive sensory changes and underlying multiple channelopathies, and suggest novel directions for biomarker search and design of multifaceted strategies for disease management.

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Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.02/X5

Topic: C.05. Neuromuscular Diseases

Support: Target ALS Grant

Title: Urate mitigates motor neuron toxicity of astrocytes derived from ALS linked SOD1 G93A mutant mice

Authors: *R. BAKSHI[1], K. TSIORAS[2], Y. XU[1], X. CHEN[1], E. GRANUCCI[1], K. A. MUELLER[1], A. DIOS[1], S. PAGANONI[1], G. SADRI-VAKILI[1], E. KISKINIS[2], M. A. SCHWARZSCHILD[1]
[1]Neurol., Massachusetts Gen. Hosp., Boston, MA; [2]Neurol., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Dominant mutations in an antioxidant enzyme superoxide dismutase-1 (SOD1) cause amyotrophic lateral sclerosis (ALS), an adult-onset neurodegenerative disease that is characterized by loss of motor neurons. Astrocytes derived from ALS patients or from the SOD1 G93A mouse model play a significant role in the specific degeneration of spinal motor neurons in ALS through a non-cell-autonomous process. Oxidative stress, whether as a primary cause of disease or a secondary consequence, has also been linked to many of these processes and is likely a central mechanism of motor neuron death in ALS. Therefore, targeting both oxidative stress and astrocyte dysfunction may offer a promising therapeutic strategy for slowing the progression of ALS. Our recently published findings demonstrate that urate (a.k.a. uric acid), a major endogenous antioxidant and a biomarker of favorable ALS progression rates, can act through astrocytes by engaging an antioxidant signaling system orchestrated by nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. We have also shown that urate protects dopaminergic neurons in cellular models of Parkinson's disease. Together, these findings paved the way for the current study where we evaluated urate's protective potential in cellular and animal models of ALS. Here we report on the neuroprotective effects and mechanisms of urate in a murine cell culture model of ALS. Primary astrocytes derived from either mutant *SOD1* G93A (expressing high copy number mutant *SOD1* transgene) and controls were treated with varying concentrations of urate or vehicle. We confirmed a significant toxic effect of conditioned medium from mutant astrocytes derived from the *SOD1* G93A transgenic mouse on motor neuron cell viability. More importantly, urate treatment had a significant protective effect on the differentiated motor neuron cell line as demonstrated by increased cellular viability. Our results suggest that urate may decrease vulnerability of motor neurons to cellular injury evoked by mutant astrocytes or oxidative stress. Further study of the molecular mechanisms of urate

protection and the role of Nrf2 pathway may substantiate the rationale for urate-elevating therapeutic strategies while suggesting novel Nrf2 pathway-activating approaches for treating motor neuron disease.
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Disclosures: R. Bakshi: None. **K. Tsioras:** None. **Y. Xu:** None. **X. Chen:** None. **E. Granucci:** None. **K.A. Mueller:** None. **A. Dios:** None. **S. Paganoni:** None. **G. Sadri-Vakili:** None. **E. Kiskinis:** None. **M.A. Schwarzschild:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.03/X6

Topic: C.05. Neuromuscular Diseases

Support: R21 NS093244-01

Title: Role of connexin 43 in disease progression and motor neuron toxicity in a rodent model and human iPS astrocytes in Amyotrophic Lateral Sclerosis

Authors: *A. A. ALMAD[1], C. WELSH[3], Y. HAO[3], A. PATANKAR[3], J.-P. RICHARD[2], S. GROSS[2], N. J. MARAGAKIS[4]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting in progressive degeneration of motor neurons (MN) in the brain and spinal cord leading to weakness and death. Astrocytes play a critical role in ALS and contribute to MN death demonstrated from studies both *in vitro* and *in vivo.* Here, we investigate a potential mechanism through which astrocytes lead to MN toxicity and disease progression. Astrocytes are interconnected through connexins (Cx) to form hemichannels and gap junctions. Cx43 is a major astrocyte connexin conducting crucial homeostatic functions. Our recent work demonstrates Cx43 is significantly elevated in rodent and notably in post-mortem human ALS tissues. We further observed that Cx43 blockers confer neuroprotection in a rodent MN-astrocyte co-culture. To understand the role of Cx43 *in vivo*, we used the $SOD1^{G93A}$ mouse model and generated a transgenic mouse line with conditional loss of Cx43 in astrocytes using a human GFAP-Cre driver mouse line referred as $SOD1^{G93A}$::Cx43 KO mice. We conducted survival, behavioral and histological studies on $SOD1^{G93A}$::Cx43KO mice. We examined that specifically deleting Cx43 in astrocytes resulted in a modest yet significant prolongation in survival of $SOD1^{G93A}$ mice. We tested motor function in the mice using grip strength analysis and observed that compared to $SOD1^{G93A}$ mice, $SOD1^{G93A}$::Cx43KO mice displayed significantly conserved forelimb grip

strength while hindlimb function was comparable between the two groups. We further examined the preservation of MNs at different stages of disease progression and observed no change in number of MNs in the lumbar spinal cord, however, a significant preservation of MNs was observed in the cervical cord of $SOD1^{G93A}$::Cx43KO mice compared to control $SOD1^{G93A}$ mice. Our *in vitro* studies show blocking Cx43 results in MN protection and *in vivo* studies implicate that Cx43 is potentially involved in disease progression in the $SOD1^{G93A}$ mice. Current studies are focused on modeling ALS using human iPS astrocytes to understand the role of astrocyte Cx43 in sporadic forms of ALS and dissect its role in disease progression. We are also investigating potential mechanisms through which Cx43 mediates toxicity on MNs. These studies have widespread implications in not just ALS but also other neurodegenerative diseases involving astrocyte mediated effects.

Disclosures: **A.A. Almad:** None. **C. Welsh:** None. **Y. Hao:** None. **A. Patankar:** None. **J. Richard:** None. **S. Gross:** None. **N.J. Maragakis:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.04/X7

Topic: C.05. Neuromuscular Diseases

Support: JSPS KAKENHI Grant Number JP15K07918

Title: FUS regulates the expression of snRNP70 by binding to its conserved intron in neuron

Authors: *T. NAKAYA
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Abstract: FUS/TLS, fused in sarcoma/translocated in liposarcoma, is one of causative factors of Amyotrophic lateral sclerosis, ALS. FUS is a nuclear RNA binding protein and has seven domains such as QGSY-rich, Gly-rich, RNA recognition motif (RRM), Arg-Gly-Gly1 (RGG1), Zinc finger, RGG2 and nuclear localization signal (NLS). It has been reported that many ALS-linked mutations found in FUS located at its carboxyl-terminal end, around its NLS, which caused abnormal cytoplasmic localization and the aggregates of FUS were usually found in cytoplasm of affected neurons of patients. Based on those observations, it is speculated that the disturbance of nuclear functions of FUS might be a cause of ALS.
Several studies have reported about the nuclear functions of FUS using High throughput sequencing of RNA isolated by UV crosslink and immunoprecipitation (HITS-CLIP) and RNA-seq of FUS knock down or knock out cells that FUS was involved in the processing of pre-mRNA including determination of their length, splicing and polyadenylation. We previously reported using HITS-CLIP on human brains and mouse ES cell derived neurons coupled with

TotalRNA-seq of FUS knock down mouse neurons that FUS had a lot of target genes by binding to their introns, especially on conserved introns and affected their expressions (Nakaya, RNA. 2013). SnRNP70 is one of those targets containing conserved introns. Here, I tried to identify the domains of FUS required for the regulation of expression of snRNP70 and found that RRM of FUS was a key domain for it. In this presentation, I will report results of further analyses and propose how FUS regulates the expression of snRNP70.

Disclosures: T. Nakaya: None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.05/X8

Topic: C.05. Neuromuscular Diseases

Title: Identification of domains required for aggregation of FUS in neuron

Authors: *D. KAWAHARA[1], T. SUZUKI[2], T. NAKAYA[3]
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Abstract: FUS/TLS, fused in sarcoma/translocated in liposarcoma is known as a causative factor of Amyotrophic lateral sclerosis (ALS). So far, many familial mutations have been found in FUS/TLS gene, and the resultant mutated proteins are believed to be neurotoxic. However, it is still unclear how those mutants show their toxicity in neurons. One of pathological features of mutants is aggregation and several reports have indicated that FUS mutants were aggregation prone proteins. Since not only mutants but also wild type (WT) FUS protein shows aggregates in affected neurons of patients, it is believed that the aggregates are critical to the pathogenesis of FUS related disorder.
In order to identify domains of FUS required for its aggregation, we employed R495X mutant, which was a familial mutation found in FUS. R495X with deletions of each domain were expressed in neurons and observed the ability of aggregation. R495X showed strong aggregates in the cytoplasm of neurons. When R495X without RRM or ZnF were expressed, they formed aggregates similar to R495X in this condition. While when R495X without Gly-rich, RGG1 or RGG2 were expressed, all of them showed almost no aggregates in neurons, indicating that any of those domains are required to form aggregates of R495X. Some previous reports demonstrated that RGG2 regulated nuclear localization of FUS WT through its methylations. Moreover, recently attractive observations were reported that the low complexity domain of FUS in its amino-terminal region including a part of Gly-rich region had a property to form a hydrogel in vitro and in vivo by increasing its concentration. Our results with these reports suggest that those domains are critical not only for the function and localization of FUS WT but also the structural

property of R495X with common intramolecular mechanism. We will present further analyses and discuss how R495X forms aggregates in neurons.

Disclosures: D. Kawahara: None. **T. Suzuki:** None. **T. Nakaya:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.06/X9

Topic: C.05. Neuromuscular Diseases

Support: MRC grant MR/M010864/1

Title: Inhibition of arfaptin 2 improves cell survival in Amyotrophic lateral sclerosis (ALS)

Authors: *K. NING, A. MOHAMMEDEID, S. KONG, S. KONG, A. J. GRIERSON, P. J. SHAW, M. AZZOUZ
Sheffield Univ., Sheffield, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder. ALS is characterized by the loss of lower and upper motor neurons (MNs) in the brain and spinal cord enlargements, with astrocytic gliosis, and the presence of ubiquitinated inclusions in the surviving motor neurons (MNs). Although the role of protein aggregates in the pathogenesis of neurodegeneration is unknown, the capacity of the proteasome system to degrade proteins may be a limiting factor in the vulnerability of neurons to the degenerative process. Proteasome activity is impaired in ALS, therefore activation of the proteasome pathway would be beneficial to ALS. Arfaptin-2, a downstream effector of ADP-ribosylation factors (ARFs), was identified as a novel protein and it is a target protein for GTP-ARFs and for GDP-Rac1. Our previous studies showed that Arfaptin 2 regulates the aggregation of mutant huntingtin protein by inhibiting proteasome activities and a dominant negative form of Arfaptin-2 (HC-ARFIP2) has been shown to maintain the proteasome activity and induce degradation of misfolded proteins (Nature Cell Biology 2002). The current study investigates the possibility of targeting protein aggregation pathway for treatment in ALS. Modulation of this pathway is approached through targeting Arfaptin-2 protein. Here we show that overexpression of HC-ARFIP2 improves cell survival in $SOD1^{G93A}$ stable NSC34 cells ($P<0.05$, n=3) and in primary cultured motor neurons from $SOD1^{G93A}$ mouse embryos ($P<0.01$, n=3). The prosurvival effect was observable even in cells treated with H_2O_2 in both $SOD1^{G93A}$ transgenic and non-transgenic motor neurons ($P<0.01$, n=3). A further investigation on the pathway of which HC-ARFIP2 exerts its neuroprotective effect showed that HC-ARFIP2 induces AKT phosphorylation. In addition, protein degradation pathway-markers (p62, LC3II, ULK1) showed significant changes ($P<0.01$, n=3) in response to HC-ARFIP2 expression. In conclusion, the study presented here has provided a proof of concept

that Arfaptin-2 is involved in protein aggregation in ALS. A dominant negative form of Arfaptin-2 improves motor neuron survival *in vitro* through activation of AKT activity. Acknowledgments: This work is supported by the Medical Research Council (MRC).

Disclosures: K. Ning: None. **A. Mohammedeid:** None. **S. Kong:** None. **S. Kong:** None. **A.J. Grierson:** None. **P.J. Shaw:** None. **M. Azzouz:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS091540

ALS Association

University of Wisconsin Foundation

Title: C9ORF72-associated pathological characteristics in skeletal muscle cells derived from ALS patient iPS cells

Authors: E. LYNCH[1], V. BELSITO[1], T. SAITO[2], T. J. HIRANO[2], J. JEFFREY[1], *M. SUZUKI[3]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease featuring degeneration of upper and lower motor neurons as well as skeletal muscle atrophy and wasting. Clinically, patients experience gradual paralysis culminating in death from respiratory failure. A hexanucleotide repeat expansion in the *C9ORF72* gene was recently discovered as the most common genetic mutation linked to ALS. Most of the research progress on this topic has been investigated within the context of the central nervous system. In contrast, it has not yet been fully elucidated how the *C9ORF72* mutation influences pathology in the skeletal muscle. The objective of this study was to use induced pluripotent stem (iPS) cells derived from ALS patients to determine some of the pathological mechanisms of the *C9ORF72* repeat expansion in skeletal muscle. We prepared myogenic progenitors and skeletal myocytes from patient-derived iPS cells using a free-floating spherical culture protocol that was recently established in our laboratory. The expression of myogenic markers (Pax7, MyoD, and Myogenin) was confirmed in the progenitors by immunocytochemistry. The progenitors were then terminally differentiated into mature myotubes for 2-12 weeks. Next, we determined whether these muscle cells would

demonstrate *C9ORF72*-associated pathology. Specific cellular features that were studied in the myotubes include changes in C9ORF72 protein expression, the presence and localization of dipeptide repeat (DPR) proteins, and abnormal protein aggregates expressing TDP-43, p62, and ubiquitin. Furthermore, electron microscopy was used to characterize pathological features at an ultrastructural level in the differentiated cells. Examples of these include abnormal organelle structures and possible pathological aggregations. Lastly, we asked whether the *C9ORF72* mutation altered sensitivity to oxidative stress. Myogenic progenitors with the *C9ORF72* mutation showed increased cytotoxicity after treatment with hydrogen peroxide or a free radical-generating agent. Together, this study shows the utility of skeletal myocytes derived from ALS-patient iPS cells for *in vitro* disease modeling, and sheds some light on how skeletal muscle is influenced by the *C9ORF72* repeat expansion.

Disclosures: E. Lynch: None. **V. Belsito:** None. **T. Saito:** None. **T.J. Hirano:** None. **J. Jeffrey:** None. **M. Suzuki:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

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Program#/Poster#: 135.08/X11

Topic: C.05. Neuromuscular Diseases

Support: NIH

ALS Association

Robert Packard Center for ALS Research

Muscular Dystrophy Association

ALSFAC

Title: Mechanistic insights into C9orf72 mediated disruptions in nucleocytoplasmic transport and the nuclear pore complex

Authors: *A. N. COYNE[1], J. G. DAIGLE[1], J. GRIMA[2], L. R. HAYES[3], J. D. ROTHSTEIN[1]
[1]Neurology, Brain Sci. Inst., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Neurosci., Johns Hopkins University, Sch. of Med., Baltimore, MD; [3]Sch. of Med., Johns Hopkins Univ., Baltimore, MD

Abstract: The motor neuron disease Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), the second most common form of early-onset dementia, comprise a spectrum of fatal neurodegenerative diseases. Clinically, multiple genetic loci have been linked to both

ALS and FTD including C9orf72. An intronic GGGGCC hexanucleotide repeat expansion (HRE) in the C9orf72 gene is the most common cause of familial ALS and FTD. This repeat is bidirectionally transcribed to form G_4C_2 and C_4G_2 RNA species which have been shown to accumulate into RNA foci. Furthermore, Repeat Associated Non-ATG (RAN) translation produces five dipeptide repeat (DPR) species from sense and antisense RNA. Together, both toxic RNA and DPRs are thought to contribute to a gain of toxicity mechanism in disease. Recently multiple labs simultaneously reported defects in nucleocytoplasmic transport as a fundamental pathway underlying C9orf72 mediated toxicity. However, the precise mechanisms underlying disruptions in nucleocytoplasmic transport, the organization and structure of nuclear pore complexes, and pathologic alterations induced by sense vs antisense RNA and DPR proteins remain largely unknown. Here, we use a combination of biochemical, immunofluorescence, super resolution and live imaging approaches in HEK293 cell, mouse, and iPS neuron models to determine the effects of DPRs on the integrity of nuclear pore complexes and the functional consequences of these disruptions. Using antisense oligonucleotides (ASOs), we assess the relative contribution of sense and antisense DPRs to disease relevant nuclear pore complex and transport phenotypes. These studies are providing novel insights into the structural organization of nuclear pore complexes, functional consequences of disrupted nuclear pores, and the toxic functions of sense and antisense RNA and DPR species in the pathogenesis of ALS/FTD.

Disclosures: A.N. Coyne: None. **J.G. Daigle:** None. **J. Grima:** None. **L.R. Hayes:** None. **J.D. Rothstein:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Program#/Poster#: 135.09/X12

Topic: C.05. Neuromuscular Diseases

Support: MNDA Grant Wade-Martins/Oct13/6201

Title: Cell targeted phenotyping: Understanding molecular genetic mechanisms of C9ORF72 ALS in motor neurons

Authors: *S. BURLEY[1], *S. BURLEY[1], O. CORDERO LLANA[3], D. BECCANO-KELLY[1], S. COWLEY[2], R. WADE-MARTINS[1]
[1]Dept. of Physiology, Anat. and Genet., [2]Sir William Dunn Sch. of Pathology, Univ. of Oxford, Oxford, United Kingdom; [3]Sch. of Clin. Sci., Univ. of Bristol, Bristol, United Kingdom

Abstract: Amyotrophic lateral sclerosis (ALS) presents in adulthood with the loss of both upper and lower motor neurons. In 2011, a large hexanucleotide repeat expansion in the C9ORF72 gene was implicated in 7% of sporadic and 40% of familial cases, making this mutation the most

frequent cause of ALS known to date.
The differentiation of lower motor neurons from induced pluripotent stem cells derived from patients with the C9ORF72 expansion provides a model allowing exploration of the downstream effects of the expansion whilst maintaining the patient's genetic background. We have successfully generated high percentage motor neuron cultures from healthy individuals and patients in vitro. These cells are electrophysiologically active and express mature motor neuron markers including choline acetyltransferase and SMI-32. We compared methods and supplements to further increase the electrophysiological maturity of the cells allowing them to resemble physiological motor neurons as closely as possible. We saw a decrease in resting membrane potential when conditions were modified.
Our electrophysiological analysis focuses on the intrinsic properties of the cells as they mature in culture including: voltage gated sodium and potassium channel current, synaptic vesicle release and action potential characteristics. Further studies will look more specifically at channel subtypes present within the patient vs control motor neurons. A HB9:cre/lox lentiviral system to drive the expression of channelrhodopsin allows us to specifically track and stimulate the motor neurons non-invasively.
Overall this project aims to further elucidate C9ORF72 disease pathophysiology to allow future development of therapeutic approaches and targets.

Disclosures: S. Burley: None. **O. Cordero Llana:** None. **D. Beccano-Kelly:** None. **S. Cowley:** None. **R. Wade-Martins:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Program#/Poster#: 135.10/X13

Topic: C.05. Neuromuscular Diseases

Support: NIH - NINDS R00 support for AH

MDA support for DT

Title: Distinct dynamics and cellular properties of dipeptide repeats derived from the C9orf72 nucleotide repeat expansion

Authors: *A. R. HAEUSLER[1], X. WEI[1], T. WESTERGARD[1], K. RUSSELL[1], M. MARKS[2], K. OZCAN[1], Y. PANG[1], C. J. DONNELLY[2], P. PASINELLI[1], D. TROTTI[1]
[1]Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Dept. of Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The expansion of a nucleotide repeat, GGGGCC, in a non-coding region of the *C9orf72* gene is the most common genetic association for two devastating neurodegenerative diseases – amyotrophic lateral sclerosis (ALS) and frontal temporal dementia (FTD). Patients affected by the *C9orf72* nucleotide repeat expansion (NRE) mutation can carry up to thousands of repeats, while non-affected individuals typically carry between 2-8 repeats. In patients harboring the *C9orf72* mutation, the expanded repeats are found to form RNA foci and the repeat-containing RNA can undergo unconventional translation in the absence of an AUG start codon called repeat associated non-ATG initiated (RAN) translation. The RAN translation of the GGGGCC repeats can generate five unique dipeptide repeat (DPR) products, G-A, G-P, G-R, P-A, and P-R, which have been identified in *C9orf72* mutation models and/or patient cells/tissues, and have been possibly linked to disease progression. Our laboratory and others have demonstrated that these DPRs cause neurotoxicity *in vitro* and *in vivo* by using codon randomization strategies to express different DPRs through classical translation. Here, we have expanded upon our previous findings employing new cell model systems that more naturally mimic the pathophysiologically relevant features identified patients harboring the *C9orf72* NRE mutation by expressing DPRs via the unconventional RAN translation of the GGGGCC repeats. Using this new DPR reporter model system, we have explored and identified the relationship among: the differential dynamic properties of the unique DPRs, the subcellular localizations, and the variability among different cell types. Our preliminary results provide a deeper mechanistic insight into a possible linkage between DPRs and *C9orf72* NRE-linked neurodegeneration.

Disclosures: A.R. Haeusler: None. **X. Wei:** None. **T. Westergard:** None. **K. Russell:** None. **M. Marks:** None. **K. Ozcan:** None. **Y. Pang:** None. **C.J. Donnelly:** None. **P. Pasinelli:** None. **D. Trotti:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: NIH Grant R21-NS090912

Muscular Dystrophy Association

Farber Family Foundation

Title: Cell-to-cell transmission of c9orf72 linked dipeptide repeat proteins

Authors: *T. R. WESTERGARD[1], B. K. JENSEN[2], X. WEN[5], J. CAI[3], E. KROPF[4], L. M. IACOVITTI[1], P. PASINELLI[6], D. TROTTI[7]

[2]ALS Weinberg Ctr., [3]Farber Inst. Neurosci, Dept Neurosci, [4]Neurosci., [1]Thomas Jefferson Univ., Philadelphia, PA; [5]Dept. of Neurosci., Farber Inst. For Neurosciences, Thomas Jefferson Univ., Philadelphia, PA; [6]Thomas Jefferson Univ., Farber Inst. Neurosci, Philadelphia, PA; [7]Neurosci., Dept. of Neurosci., Philadelphia, PA

Abstract: Intronic hexanucleotide repeat expansions in the C9orf72 gene are the most common genetic cause for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). RNA transcripts of these expansions can undergo RAN translation to form five dipeptide repeat proteins (DPRs): poly(GA), poly(GP), poly(GR), poly(PA), and poly(PR). DPR aggregates are found throughout the CNS of C9orf72-ALS/FTD patients and cause neuronal degeneration and dysfunction in cell and animal models. While DPR toxic mechanisms continue to be investigated, the potential for DPR aggregates to spread has yet to be determined. Utilizing different experimental platforms, including spinal motor neurons derived from induced pluripotent stem cells from C9orf72-ALS patients, we found evidence for cell-to-cell transmission for each DPR with varying frequencies and modality of spreading. One mechanism behind transmission is via exosomes. Exosomes isolated from DPR-expressing cells showed varying amounts of DPRs and evidence of transmission to neurons. DPR transmission also occurred through exosome-independent pathways. These studies demonstrate cell-to-cell transmission of C9-DPRs, which is potentially relevant to disease.

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Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: MDA

NIH R21-NS090912

Farber Family Foundation

Title: C9orf72 RAN-translated poly-GA peptides result in perturbed neuronal signaling and delayed cell death in mature primary neurons

Authors: *B. K. JENSEN[1], X. WEN[1], K. KRISHNAMURTHY[1], B. CURRAN[2], T. WESTERGARD[1], L. MA[2], A. HAEUSLER[1], P. PASINELLI[1], D. TROTTI[1]
[1]ALS Weinberg Ctr., [2]Vickie and Jack Farber Inst. for Neurosci., Thomas Jefferson Univ., Philadelphia, PA

Abstract: An intronic hexanucleotide repeat expansion (G4C2) in the C9Orf72 gene is the most frequent genetic cause for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Five dipeptide repeat proteins (DPRs) are produced by RAN-translation from this expansion, with the most abundantly detected in patient tissue being poly-glycine-alanine (GA). Two mouse models have independently demonstrated motor deficits stemming from poly-GA expression in neurons by 6 months of age. When confined to the cortex, poly-GA_{50} leads to neuronal loss, brain atrophy, motor and cognitive behavioral deficits. When expressed in spinal cord and brainstem, poly-GA_{149} triggers pronounced motor deficits in the absence of overt neuronal loss. These findings highlight the necessity for a deeper understanding of subcellular repercussions in neurons coping with poly-GA peptides, as evidence suggests that *in vivo* motor deficits may precede cell death of affected neurons. Poly-GA expression in immature primary neurons results in reduced neurite outgrowth and cellular toxicity through proteasome impairment and ER stress. However, the consequences of poly-GA on neuronal signaling events have not yet been examined in mature primary neurons with functional synaptic connectivity. We hypothesized that poly-GA dipeptides may cause a delayed degeneration through disruption of neuronal signaling and impairment of synaptic transmission.
FLAG-GFP-fused poly-GA of various repeat lengths was transfected into mature primary rat cortical and motor neurons. Using longitudinal live-cell imaging, survival analysis indicates that compared with the overtly toxic arginine-rich DPRs, poly-GA containing cells display a delayed toxicity profile. At timepoints greatly preceding cell death, confocal microscopy revealed length-independent poly-GA aggregates in cytosolic, axonal, and dendritic regions. High-resolution live-cell imaging using a spinning-disk confocal microscope showed that GA-puncta are mobile within neurites, with these puncta becoming increasingly stationary as GA-repeat length increased. Using this microscopy platform and commercially available kits, the mobility and function of multiple organelles was also investigated in GA-containing primary neurons and motor neuron-like NSC-34 cells. Finally, poly-GA aggregates within neurites suggested the potential for abnormalities in synaptic transmission. Using a FM4-64 dye-unloading assay to approximate levels of evoked synaptic vesicle release, we found that this capacity in neurons harboring poly-GA aggregates is significantly diminished.

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Poster

135. Motor Neuron Disease: *In Vitro* Studies

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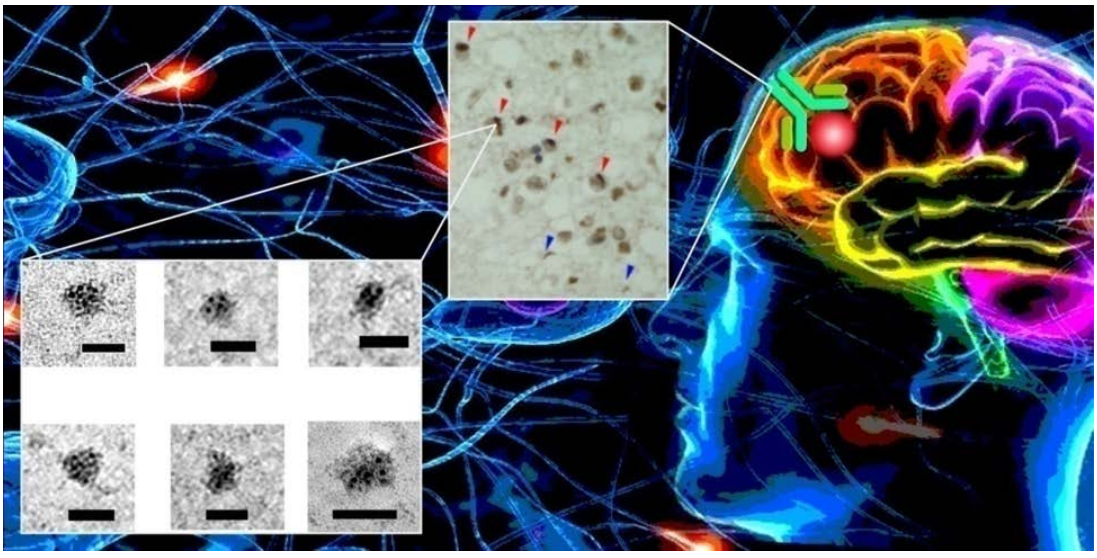
Topic: C.05. Neuromuscular Diseases

Support: MoST, Taiwan, 105-2314-B-001 -008 -MY3

Title: Understanding TDP-43 oligomers and dipeptide repeats in neurodegenerative diseases

Authors: *Y.-R. CHEN
Genomics Res. Center/Academia Sinica, Taipei, Taiwan

Abstract: Inclusions comprising TDP-43 and dipeptide repeated (DPR) translated from hexanucleotide expansions in C9ORF72 gene were found in frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). The diseases affected different brain regions but have some overlapping symptoms. C9ORF72 hexanucleotide expansion can be translated to DPRs, including poly glycine-alanine (GA), glycine-arginine, glycine-proline, proline-arginine, and proline-alanine, which form inclusions in brain and spinal cord of C9ORF72-linked FTD/ALS patients. The structure and function of both TDP-43 and DPRs have not been elucidated. Hence, we employed biochemistry and cellular methods to examine TDP-43 oligomers and DPRs. We first discovered that full-length TDP-43 oligomers are present in brain of FTD-TDP and ALS patients. The full-length TDP-43 forms spherical oligomers that share common epitopes with amyloid oligomers. The TDP-43 oligomers are neurotoxic and capable to transform Alzheimer's amyloid-β (Aβ) to Aβ oligomers. Furthermore, we generated a TDP-43 oligomer specific antibody, TDP-O, specifically targeting TDP-43 oligomers, but not native TDP-43 (Nature Communications, 2014, 5:4824). Initial intravenous injection of monoclonal TDP-O antibody to mice showed efficacy to rescue TDP-43 induced toxicity. Meanwhile, we used synthetic poly (GA)15 DPR as a model system to examine its aggregation properties (J Biol. Chem., 2016, 291(10):4903-11). We found that (GA)15 with 15 dipeptide repeats fibrillates rapidly to flat, ribbon-type fibrils. The fibrils bind to classic amyloid dyes and contain characteristic cross β-sheet structures. We also demonstrated that (GA)15 DPR is neurotoxic and capable of cell-to-cell transmission. Overall, our results provide structural and toxicity properties of TDP-43 oligomers and GA DPR and a specific antibody to facilitate future therapeutic development.



Disclosures: Y. Chen: None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Support: NIH Grant R01 NS090335

NIH Grant R01 NS076919-01

Grant from Kennedy's Disease Association

Title: Role of USP7 in the pathogenicity of spinal and bulbar muscular atrophy

Authors: *A. PLUCIENNIK, T. BERGER, D. MERRY
Thomas Jefferson Univ., Philadelphia, PA

Abstract: Spinal and bulbar muscular atrophy (SBMA) is characterized by a loss of brain stem and spinal cord motor neurons, and of the associated innervated muscles. This toxicity to the neuromuscular system is caused by the expansion of a CAG repeat-encoded polyQ segment within the androgen receptor protein, a transcription factor that is activated by its cognate ligands, testosterone and dihydrotestosterone. Although the molecular events that mediate expanded-polyQ-dependent toxicity remain largely obscure, such long polyQ tracts may cause cellular dysfunction and ultimately cell death by dysregulating protein-protein interactions that sustain normal cellular function. Therefore, to understand this dysregulation, we have employed a quantitative proteomics approach involving stable isotope labeling of amino acids in cell culture (SILAC) to identify changes in the AR protein interaction network caused by polyQ expansion. One of the top hits identified was the ubiquitin-specific protease USP7, which we have validated as a preferential interactor with polyQ-expanded AR. We also observed that USP7 interacts with polyQ-expanded AR in SBMA transgenic mice. This protein preferentially interacts with soluble AR, and does not colocalize with AR nuclear inclusions. Moreover, reduction of USP7 levels by shRNA-mediated gene silencing in polyQ-expanded AR-expressing cells decreased the frequency of nuclear inclusions and cytotoxicity. Consistent with these findings, overexpression of wild-type, but not catalytically inactive, USP7 resulted in a dramatic increase in polyQ-expanded AR aggregation as well as cytotoxicity. Using the proximity ligation assay, we also showed that partial knockdown of USP7 results in increase in ubiquitination of polyQ-expanded AR, suggesting direct action of USP7 on AR. These findings support the idea that the deubiquitinase function of USP7 plays a role in polyQ-expanded AR toxicity, and that inhibiting USP7 activity may be a viable therapeutic strategy for the treatment of SBMA. We are currently assessing the effect of pharmacological inhibitors of USP7 on polyQ-expanded AR aggregation and toxicity.

Disclosures: **A. Pluciennik:** None. **T. Berger:** None. **D. Merry:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.15/X18

Topic: C.05. Neuromuscular Diseases

Support: KAKENHI

Title: USP15 regulates RNA splicing through deubiquitination of TUT1

Authors: ***J. KIM**[1], F. TSURUTA[2], T. CHIBA[3]
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Abstract: Alternative pre-mRNA splicing plays an important role in protein diversity and complexity. It enables eukaryotic cells to produce a huge number of proteins from restricted genes through the selective elimination of introns and exon rejoining, and thereby contributes to tissue-specific gene functions. In brain, alternative splicing constitutes the basis for neuronal functions regulated by gene expression. Given the importance of alternative mRNA splicing in regulating neuronal functions, it is hardly surprising that disruption of RNA splicing leads to neuronal dysfunction. Indeed, recent studies have revealed that disruption and misregulation of RNA splicing result in neuromuscular disorders such as amyotrophic lateral sclerosis and spinal muscular atrophy. However, the molecular mechanism of how the failure in RNA splicing leads to neuromuscular disorder is yet to be elucidated. In this study, we found that deubiquitinating enzyme, ubiquitin specific peptidase 15 (USP15), is associated with neuromuscular functions via the control of RNA splicing. USP15 deficient mice exhibit ataxia-like behaviors resulting from the morphological defect of cerebellum and skeletal muscle. USP15 binds to SART3 and deubiquitinates TUT1, terminal uridylyl transferase 1, which is responsible for U6-snRNA polyuridylation, resulting in changes in subnuclear localization and transferase activity of TUT1. Furthermore, loss of USP15 widely affects splicing patterns of substantial genes potentially associated with neuromuscular disorders. Taken together, these data suggest that loss of USP15 may bring about aberrant gene expression mediated by misregulation of RNA splicing through deubiquitination of TUT1, and thereby impairs neuromuscular functions. Therefore, this study is expected to be a novel clue for clarifying the relationship between mRNA splicing and neuromuscular diseases.

Disclosures: **J. Kim:** None. **F. Tsuruta:** None. **T. Chiba:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.16/X19

Topic: C.05. Neuromuscular Diseases

Support: Project A.L.S.

Title: Modeling ALS with stem-cell-derived spinal and cranial motor neurons possessing differential vulnerability

Authors: *D. AN[1], D. E. IANNITELLI[2], M. AL-SAYEGH[4], I. YAGUDAYEVA[5], E. MAZZONI[3]
[1]Biol., [3]Dept. of Biol. and Neurosci. Inst., [2]New York Univ., New York, NY; [4]Biol. Div., New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates; [5]Columbia Univ., New York, NY

Abstract: Amyotrophic lateral sclerosis (ALS) is a common motor neuron disease characterized by progressive degeneration of mainly spinal motor neurons (SMN), which leads to muscle atrophy and eventual death of the patients. Despite unclear pathogenesis from many different genetic mutations and suspicious environmental risk factors, there is a common spare of a subset of cranial motor neurons (CMN) in ALS. Understanding the nature of CMN resistance to ALS promises to open a new frontier for the study of ALS pathology and the development of therapeutic strategies. However, the study of differential vulnerability between SMNs and CMNs has been limited by the access to large and homogenous population of CMNs. Taking advantage of direct programming using transcription factors NIL (Ngn2-Isl1-Lhx3) and NIP (Ngn2-Isl1-Phox2a), we can differentiate SMNs and CMNs respectively from mouse embryonic stem cells (ESC) in a highly efficient and scalable way. To test their response to ALS toxicity, we established isogenic inducible lines to program SMNs and CMNs expressing same level of human SOD1 proteins: wild type hSOD1 and ALS mutant hSOD1 A4V and G93A, which are well-studied ALS mutations in mouse and *in vitro* models. Survival assays showed that ESC-derived CMNs are more resistant than SMNs to the overexpression of hSOD1 G93A mutant proteins, consistent with the differential vulnerability of SMN and CMN in ALS patients. On one hand, Western Blot study of hSOD1 proteins revealed higher accumulation of ALS mutant hSOD1 proteins in SMNs than CMNs and treatment of proteasome inhibitor reversed the result, suggesting that CMNs deal with ALS hSOD1 proteins better than SMNs using a different mechanism. On the other hand, we found that CMNs were more resistant than SMNs to proteostatic stress caused by CPA and Tunicamycin, which implies that CMNs not only accumulate less hSOD1 ALS mutant proteins, but also are more resilient to the stress caused by misfolded hSOD1 ALS mutants. These results suggest that the ESC-derived SMNs and CMNs

can serve as a good ALS *in vitro* model and that their difference in proteostasis capacity may explain the differential susceptibility of SMN and CMN to ALS neurodegeneration.

Disclosures: D. An: None. **D.E. Iannitelli:** None. **M. Al-Sayegh:** None. **I. Yagudayeva:** None. **E. Mazzoni:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

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Program#/Poster#: 135.17/X20

Topic: C.05. Neuromuscular Diseases

Support: 5T32GM007367-38

Title: Retromer complex deficiency in amyotrophic lateral sclerosis astrocytes

Authors: *E. J. PEREZ-TORRES[1,2], V. MISHRA[1], D. E. BERMAN[1], S. A. SMALL[2], F. LOTTI[1], S. PRZEDBORSKI[1,2]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disease that results in the death of motor neurons (MNs) in the spinal cord and brain. While ALS is usually sporadic (sALS), transgenic (Tg) mice expressing mutant genes associated with the familial form effectively model the disease. One such model expresses a G93A mutation in SOD1 ($SOD1^{G93A}$). Mounting evidence both in vivo and in vitro has shown that astrocytes play an integral role in this neurodegeneration. New data indicate that protein trafficking and processing defects are likely involved in non-cell-autonomous MN degeneration. Here, we study the possible contribution of the retromer complex to these defects. The retromer complex's function is to traffic proteins away from the endosome to the trans-Golgi network and to the plasma membrane. This complex has a well-established role in protein trafficking—particularly that of APP in neurons—, and defects in the retromer have been linked to multiple neurodegenerative diseases. Here, we show a marked decrease of retromer core components—VPS35, VPS26A, and VPS29—in cultured astrocytes from patients afflicted with sALS. We show a similar decrease in retromer component expression in cultured astrocytes and spinal cord extracts from $SOD1^{G93A}$-Tg mice, but not from wild-type SOD1-Tg mice. This decrease is likely due to a post-translational destabilization of the complex, as mRNA levels of all three components are significantly increased. Treatment with the retromer-stabilizing compound R33 corrects the protein levels of the core components. We further show that this retromer complex deficiency results in downstream protein processing defects of known retromer cargos. We are currently testing the hypothesis that decreased function of the retromer complex may contribute

to aberrant protein processing in astrocytes, which may, in turn, contribute to ALS neurodegeneration.

Disclosures: E.J. Perez-Torres: None. **V. Mishra:** None. **D.E. Berman:** None. **S.A. Small:** None. **F. Lotti:** None. **S. Przedborski:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.18/X21

Topic: C.05. Neuromuscular Diseases

Title: Stress granules formation upon condition of chronic stress in human als disease models

Authors: C. COLOMBRITA[1], V. GUMINA[2,1], A. MARASCHI[1], A. DORETTI[1], F. SASSONE[1], P. BOSSOLASCO[1], A. RATTI[3], *V. SILANI[3]
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Abstract: Abnormal cytoplasmic aggregates of TAR DNA binding protein (TDP-43) represent an hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) diseases, as pathological inclusions of this protein were found in autoptic brain tissues from familial and sporadic ALS and FTD patients. The RNA-binding protein TDP-43 is also an important component of stress granules (SG), reversible and dynamic cytoplasmic protein/RNA complexes which form a response to environmental stress conditions, as demonstrated for the first time by our laboratory. Recently, SGs have been hypothesized to contribute to neurodegeneration in ALS/FTD via gain or loss-of-function mechanisms. In particular, pathological inclusions containing TDP-43 are supposed to derive from SGs that, in condition of a prolonged stress as it occurs during the neurodegenerative process, fail to be properly disassembled and, by persisting in the cell, eventually interfere also with the autophagic pathway. To better investigate this hypothesis we reproduced a status of chronic stress in vitro to evaluate if SGs are able to form in this condition and not only under sub-lethal environmental insults as described in literature so far. We used primary fibroblasts obtained from skin biopsies of healthy controls and ALS patients, which were exposed to low doses (5-50uM) of sodium arsenite for a prolonged time-course (1-6 days). We observed SGs formation during chronic arsenite treatment both in control and patients fibroblasts and, in comparison to SGs forming upon acute arsenite stress (0.5 mM for 30 minutes), they were significantly larger in size as assessed by image analysis. When we used fibroblasts derived from *TARDBP* and *C9ORF72* ALS mutated patients we also found differences in SGs formation as regards both number and size in a mutant gene-dependent manner. When using iPSC-derived neurons, we confirmed the formation of SGs in both

TARDBP and *C9ORF72* cells upon arsenite exposure. Our findings demonstrate for the first time that SGs may form not only upon sub-lethal environmental stress but, importantly, also in condition of chronic and prolonged insults in human patients cells. Therefore our data seem to support the hypothesis that SGs may indeed represent an initial response to oxidative stress and that they may then be converted into pathological inclusions contributing to neurodegeneration in ALS and FTD.

Disclosures: C. Colombrita: None. **V. Gumina:** None. **A. Maraschi:** None. **A. Doretti:** None. **F. Sassone:** None. **P. Bossolasco:** None. **A. Ratti:** None. **V. Silani:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

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Program#/Poster#: 135.19/X22

Topic: C.05. Neuromuscular Diseases

Support: NIH RO1

AFM-Telethon postdoctoral fellowship

Title: Impairment of the serotonergic pathway in a mouse model of spinal muscular atrophy

Authors: *N. DELESTRÉE, E. SEMIZOGLOU, E. DROBAC, G. Z. MENTIS
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Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative genetic disease caused by a deficiency of the SMN protein. The hallmarks of the disease include degeneration of motor neurons, muscle atrophy and abnormal reflexes. Posture and spinal reflexes are dramatically impaired in both patients and animal models of SMA. However, the mechanisms involved in the impairment of motor behaviors are poorly understood.One of the descending pathways thought to govern motor behaviors is the serotonergic pathway. The serotonergic pathway exert one of the major neuromodulatory influences on spinal neurons including motor neurons. Although proprioceptive synapses on motor neurons have been shown to be one of the earliest synapses affected in the onset of disease, whether serotonergic (5-HT) modulation is also affected in SMA is currently unknown.
Here, using mouse models of SMA, we uncovered that 5-HT synapses are significantly affected in the course of disease. We found that 5-HT synaptic coverage of vulnerable motor neurons is reduced by ~50% at early stages of the disease compared to wild types. Importantly, the 5-HT synaptic reduction follows the progression of the disease. Intriguingly, synaptic loss occurs specifically in vulnerable motor neurons (innervating axial musculature), but not resistant motor

neurons (innervating distal hindlimb muscles) at the onset of the disease. Functionally, the selective stimulation of 5-HT neurons using optogenetic approaches revealed a reduced modulation of the sensory-motor reflex in vulnerable spinal segments in SMA mice.
Taken together, these results indicate that SMA is a disease of motor circuits and suggest that dysfunction of serotonergic synapses participate together with those of proprioceptive sensory neurons to the pathological events causing motor neuron dysfunction and impairment of motor behavior in mouse models of the disease.

Disclosures: **N. Delestrée:** None. **E. Semizoglou:** None. **E. Drobac:** None. **G.Z. Mentis:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

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Program#/Poster#: 135.20/X23

Topic: C.05. Neuromuscular Diseases

Support: Helmholtz Gesellschaft VH-VI-510; "RNA Dysmetabolism on ALS and FTD"

Title: Modelling FUS associated ALS pathology with human induced pluripotent stem cells and patient derived spinal motoneurons

Authors: ***J. HIGELIN**[1], M. DEMESTRE[1], A.-K. LUTZ[1], A. HERMANN[2], A. LUDOLPH[3], T. BOECKERS[1]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the degeneration of upper and lower motoneurons (MN) which leads to progressive muscle weakening and in most cases to death due to respiratory failure. In 5% of familial ALS (fALS) cases mutations in the multi domain protein FUS (Fused in Sarcoma) have been identified as a genetic cause of the disease. FUS is a RNA binding protein involved in multiple steps of gene expression such as mRNA splicing, translation and mRNA transport for local translation in dendrites. Mainly it is located in nuclei but also presents a dendritic localization and is detectable in synaptic spines in neurons. Most of the FUS mutations related with ALS are clustered in the nuclear localization signal (NLS), which is involved in the proper transport of the protein. As a result, in brain and in spinal cord of affected patients, FUS aggregates are detected in the cytoplasm. FUS is also implicated in DNA damage response by showing a direct interaction with Histone deacetylase 1 (HDAC1). This interaction is affected by FUS mutations and might lead to impaired DNA damage repair in neurons and DNA damage accumulation.
In murine models the overexpression of WT FUS has toxic effects to neurons. In this context, we

have used hiPSC-derived MNs as a suitable system to model ALS associated neuropathology. HiPSCs from different fALS-FUS patients harboring a late onset missense mutation (R521C) and two juvenile onset mutations (R495QfsX527, Asp502Thrfs*27) were generated to analyze pathophysiological phenotypes associated with these specific mutations. Cells were analyzed under physiological conditions as well as after induced DNA damage, accomplished by irradiation. Interestingly in non differentiated stem cells the vulnerability to DNA damage was dependent on the severity of the mutation and patient-derived MN showed signs of affected DNA damage response.
Similarly, mislocalization of FUS protein in MN correlated with the severity of the underlying mutation and could lead to a complete shift of nuclear FUS into the cytoplasm. Interestingly, an aberrant distribution of FUS^+ granules along the neurites, which were increased in size were also detected in patient cells. Furthermore, these FUS^+ granules along the neurites co-localized with stress granules which were also increased in size and number. These findings correlated to the patients age of onset of disease from which the cell were derived. Thus, ALS-FUS hiPSC are suitable to model ALS pathology and can be a useful tool to study specific pathophysiology in affected neurons.

Disclosures: J. Higelin: None. **M. Demestre:** None. **A. Lutz:** None. **A. Hermann:** None. **A. Ludolph:** None. **T. Boeckers:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.21/X24

Topic: C.05. Neuromuscular Diseases

Support: Target ALS

Title: Monitoring physiology of individual als ipsc-derived motor neurons through longitudinal imaging analysis

Authors: *E. BEREZOVSKI[1], J. PEREIRA[1], A.-C. DEVLIN[3], J. KOH[1], D. F. MOAKLEY[2], B. WAINGER[2]
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder of motor neurons in the brain and ventral spinal cord. 90% of ALS cases are apparently sporadic, while 10% are familial and result from mutation in one of over 30 identified ALS-causing genes. We use induced pluripotent stem cells (iPSCs) differentiated into spinal motor neurons as an in vitro model of the disease. One advantage of this approach is the ability to model sporadic

disease cases, for which mouse models are difficult to construct. Other advantages include the ability to make large numbers of motor neurons for higher throughput analyses as well as better fidelity to human genetic background. Using iPSC-derived motor neurons, prior studies have shown spinal motor neuron hyperexcitability early in culture followed by decreased motor neuron excitability in later stages. Abnormalities of motor neuron excitability, predominantly hyperexcitability, have also been demonstrated using neurophysiological techniques in ALS patients. We are developing longitudinal physiological monitoring software that will allow us to combine physiological function using calcium imaging as a surrogate of firing activity with survival analysis of individual cells, indeed determining whether prolonged and sustained calcium signal is correlated with imminent cell death. Compared with analysis of total counts of cells at different time points, this approach should improve statistical power by providing an analysis of individual cells followed over time so that a clearer distinction between cell lines can be made. The longitudinal analyses also should enable subgroup evaluation based on firing or morphological features that can be investigated on the molecular or expression levels. Together these tools will allow us to ascertain additional information about the mechanisms underlying longitudinal changes in motor neuron excitability in ALS.

Disclosures: E. Berezovski: None. **J. Pereira:** None. **A. Devlin:** None. **J. Koh:** None. **D.F. Moakley:** None. **B. Wainger:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 135.22/X25

Topic: C.05. Neuromuscular Diseases

Support: NIH Grant NS072735-02

Title: Homocysteine suppresses evoked neurotransmission and sensitizes the mouse neuromuscular junction to mild oxidative stress, as observed by a decrease in spontaneous neurotransmitter release, by activating NMDA receptors

Authors: Y. CHEN[1], *C. A. LINDGREN[2]
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Abstract: Amyotrophic Lateral Sclerosis (ALS), a neurodegenerative disease, is characterized by the progressive degeneration of motor neurons. Prior to the onset of motor neuron degeneration, reactive oxygen species (ROS) accumulate at the neuromuscular junction (NMJ) to induce oxidative-stress-mediated presynaptic decline, suggesting that ALS pathology may begin at the NMJs before progressing to the motor neurons. Previous research has shown that Homocysteine (HCY), a non-protein amino acid elevated in ALS human subjects, amplifies

ROS-induced depression of spontaneous vesicle release at the mouse diaphragm NMJ. The current study expanded on this finding by exploring the effect of HCY on both spontaneous and evoked neurotransmitter release at the mouse NMJ.
We measured end-plate potentials (EPPs) and miniature end-plate potentials (MEPPs) at the mouse epitrochleoanconeus muscle NMJ and calculated MEPP frequency and quantal content (EPP/MEPP). We found that the ROS H_2O_2 (30 min, 300 μM) alone did not affect MEPP frequency, whereas HCY incubation (3 hours, 500 μM) followed by the ROS treatment significantly decreased MEPP frequency, confirming HCY's sensitizing effect on ROS-induced depression. As shown previously, we found that AP5 (50μM), an NMDA receptor (NMDAR) antagonist, inhibited the sensitization when co-applied with HCY. We went on to demonstrate that this sensitizing effect of HCY could be mimicked by NMDA (3 hours, 20μM). These results support the hypothesis that HCY increases the sensitivity of the NMJ to mild oxidative stress as detected by a suppression of spontaneous neurotransmitter release by activating NMDA receptors at the NMJ.
In contrast to the above, the response of evoked neurotransmitter release (quantal content) to mild ROS and HCY differed from the effects on MEPP frequency. HCY alone (3 hours, 500μM) decreased quantal content, but not MEPP frequency. Furthermore, mild ROS treatment (30 min, 300 μM H_2O_2) depressed quantal content regardless of whether the preparation was incubated in HCY for three hours. Although the effect of HCY alone on quantal content was blocked by AP5, the effect of mild ROS by itself does not depend on NMDA receptors.
Collectively, our results reveal two effects of extended exposure to HCY at the mouse NMJ: First, this treatment sensitizes the NMJ to mild ROS exposure, resulting in a decrease in MEPP frequency. Second, HCY incubation *per se* depresses quantal content but not MEPP frequency. Both effects of HCY involve the NMDA receptor.

Disclosures: Y. Chen: None. **C.A. Lindgren:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: NIH STTR Grant R41TR001270

NSF STTR Grant 1622852

Title: Nerve-On-A-Chip for modelling motor neuron diseases and preclinical neurotoxicity testing

Authors: *A. D. SHARMA[1], J. Q. BEHN[2], L. A. PACE[2], J. L. CURLEY[3], M. MOORE[4]
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Abstract: Motor neuron diseases are sporadic or inherited neurodegenerative disorders that cause the progressive death of motor neurons leading to symptoms such as the loss of motor function, weakening of muscles, paralysis, and often death. Amyotrophic Lateral Sclerosis (ALS), a type of motor neuron disease, has an occurrence rate of about 0.4 to 2.4 cases per 100,000 people worldwide with an average post-diagnosis life expectancy of two to five years. Due to the complexity and relative inaccessibility of the nervous system as well as the lack of availability of human neuronal cells, preclinical testing for drugs is largely performed on animal models and immortal cell lines which are limited in their potential to mimic human disease. Following the development of induced pluripotent stem cell (iPSC) technology, it has become possible to screen a wide variety of compounds via high throughput disease-specific *in vitro* tests. Although these tests can provide information about some relevant parameters such as neurite length and cytotoxicity, these 2D *in vitro* assays lack information about many other clinically valuable data such as the presence of functional myelination or compound action potentials. Additionally, a 2D network of a cells cannot efficiently replicate human motor neurons, which can grow up to several feet long *in vivo.* To overcome the challenges associated with preclinical drug testing, we invented a 3D microengineered neuronal-glial coculture system that utilizes Rat Dorsal Root Ganglion Cells (DRGs) to mimic the structure and physiology of native peripheral nerve tissues. To expand the system's direct relevancy to human nerve tissue, we incorporated iPSC derived motor neurons, astrocytes, and primary Schwann cells to successfully create a 3D *in vitro* Human-Motor-Nerve-On-A-Chip. The 3D human motor neuron and glial coculture showed robust neurite outgrowth (>4mm) and viability when observed at one month. In addition to the dense outgrowth seen using healthy iPSCs-derived motor neurons, significant neurite growth was also found in neurons expressing the familial ALS SOD1 (G93A) mutation. Further testing is ongoing to evaluate this system for electrophysiological and myelination potential. The ability to deliver high content, clinically-relevant data will revolutionize the field of preclinical testing in efficiency, cost, and accuracy.

Disclosures: A.D. Sharma: None. **J.Q. Behn:** None. **L.A. Pace:** None. **J.L. Curley:** None. **M. Moore:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: ALS Starter Grant 17-IIP-369

SU Startup Funds

Title: Als and ubiquilin-2: Biophysical insights into ubiquilin-2 structure and function

Authors: *C. CASTANEDA[1], T. DAO[2]
[1]Biol. and Chem., [2]Syracuse Univ., Syracuse, NY

Abstract: An emerging feature of many ALS-associated proteins, particularly RNA-binding proteins consisting of low-complexity domains, is that they spontaneously demix from solution and form liquid droplets, a phenomenon generally known as liquid-liquid phase separation (LLPS). LLPS is hypothesized to be the mechanism that underlies the formation of stress granules, membraneless organelles formed under cellular stress containing sequestered RNA and proteins. Here we show that Ubiquilin-2 (UBQLN2), a member of the proteasomal degradation and autophagy pathways, phase separates into protein-containing droplets under physiological ionic strength and temperature conditions. Using NMR spectroscopy in conjunction with deletion constructs, we show that the C-terminal STI and UBA domains of UBQLN2, and the intrinsically disordered proline-rich region of UBQLN2, where most of ALS-associated mutations reside, all contribute to phase separation behavior of UBQLN2. Our studies suggest that UBQLN2 phase separation is driven by multivalent hydrophobic interactions that are promoted by UBQLN2 oligomerization. Importantly, our microscopy studies demonstrate that upon the addition of ubiquitin, UBQLN2 phase separation is eliminated, but not when a binding-incompetent Ub mutant is used. From NMR studies, we propose a model whereby Ub binding disrupts multivalent interactions involving the UBA domain of UBQLN2. We postulate that UBQLN2 phase separation behavior may be a method by which UBQLN2 is recruited to membraneless organelles, and upon interaction with ubiquitinated substrates, can traffic these proteins out of membraneless organelles for proteasomal degradation.

Disclosures: C. Castaneda: None. **T. Dao:** None.

Poster

135. Motor Neuron Disease: *In Vitro* Studies

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Topic: C.05. Neuromuscular Diseases

Support: NIH R01 NS076919-01

NIH R01 NS090335

Sigma Xi GIAR

Title: Deficient nuclear export of polyglutamine-expanded androgen receptor contributes to toxicity in spinal and bulbar muscular atrophy

Authors: *F. ARNOLD, D. E. MERRY
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Abstract: Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disease caused by a polyglutamine (polyQ) expansion in the androgen receptor (AR). Upon ligand binding of testosterone or dihydrotestosterone the AR undergoes a conformational change, inducing nuclear localization and the transcriptional regulation of target genes. In SBMA, both the presence of hormone and the nuclear localization of the AR are necessary for toxicity, with the formation of intranuclear inclusions of aggregated AR a hallmark of the disease state. Given the requirement of nuclear localization for disease-mediated toxicity, we sought to determine if the nuclear export of polyQ-expanded AR is disrupted, and, if so, whether enhancing the nuclear export of polyQ-expanded AR is protective in models of SBMA. A heterokaryon analysis of PC12 cells inducibly expressing human AR revealed that polyQ-expanded AR is deficient in nuclear export compared to wildtype AR, even prior to the formation of intranuclear inclusions. Additionally, tagging the mutant AR with an exogenous nuclear export signal (NES) reduced both inclusion formation and hormone-dependent toxicity. Mechanistically, enhancing AR nuclear export destabilizes the protein by promoting proteasomal degradation. All together, these experiments provide us with a new understanding of the role of nuclear export in SBMA pathogenesis and new insights into the effect of the polyQ-expansion on nuclear export.

Disclosures: F. Arnold: None. **D.E. Merry:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

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Program#/Poster#: 136.01/X29

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NS040408

NS078771

Title: Elevated MeCP2 in mice causes neurodegeneration involving Tau dysregulation and excitotoxicity

Authors: *J. M. FRANKLIN[1], K. R. MONTGOMERY[1], A. LOUIS SAM TITUS[2], L. WANG[1], S. R. D'MELLO[1]
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Abstract: Methyl-CpG-binding protein 2 (MeCP2), is a protein expressed from the X-chromosome that binds to methylated DNA, modifying chromatin structure to a transcriptional repressed state through the recruitment of co-repressors and histone deacetylases. More recently, it has been found to also activate gene expression by binding to promoters. Expression of the X-linked MeCP2 gene has to be carefully regulated as a modest reduction or increase in function results in serious neurological disorders.
We are studying transgenic mice in which the MeCP2 gene is expressed from its own promoter at 3 - 5 times higher than the normal level (MeCP2-Tg mice). Male MeCP2-Tg mice, but not female mice, suffer severe motor and cognitive deficits and die at around 20 weeks of age. The abnormalities displayed by MeCP2-Tg mice recapitulate those displayed by patents with MeCP2 duplication or triplication syndrome, a disorder that affects predominantly males with females as carriers. MeCP2-Tg mice display highly elevated GFAP expression within the hippocampus and cortex. The upregulation of GFAP is followed by increased Tau expression and neuronal loss in the hippocampus and cortex which occurs at about 12 weeks of age. Extensive loss of Purkinje neurons, but not of granule neurons in the cerebellar cortex is also seen at about 15 weeks. Exposure of cultured cortical neurons to conditioned medium from astrocytes (ACM) derived from MeCP2-Tg mice, or normal astrocytes in which MeCP2 is expressed at elevated levels, promotes neuronal death. Interestingly, ACM from male, but not female MeCP2-Tg mice display this neurotoxicity. ACM neurotoxicity can be completely prevented by MK-801 suggesting that it is caused by excitotoxicity. Based on the phenotypic resemblance of MeCP2-Tg mice to patients with MeCP2 duplication syndrome, we propose for the first time that that MeCP2 duplication syndrome is a neurodegenerative disorder resulting from astrocyte dysfunction leading to Tau-mediated excitotoxic loss of neurons. Loss of cortical and hippocampal neurons may explain the mental retardation and epilepsy in patients whereas ataxia may result from the loss of Purkinje neurons.

Disclosures: J.M. Franklin: None. **K.R. Montgomery:** None. **A. Louis Sam Titus:** None. **L. Wang:** None. **S.R. D'Mello:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.02/X30

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Involvement of Charcot-Marie-Tooth disease genes expression in anticancer agent-induced peripheral neuropathy in rats

Authors: *Y. YAMASHITA[1], K. IRIE[1], A. KOCHI[1], N. KIMURA[1], K. MATSUO[2], T. HAYASHI[6], T. MYOSE[1], K. SANO[1], T. NAKANO[3], Y. TAKASE[3], Y. NAKAMURA[7], T.

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Abstract: Background and Purpose: The anticancer agent such as oxaliplatin (L-OHP) or paclitaxel (PTX), often induces peripheral neuropathy including mechanical allodynia. Additionally, it has been known that L-OHP damages cellular DNA, and PTX damages axon. However, detailed mechanisms of L-OHP- and PTX-induced peripheral neuropathy have not been fully elucidated. To investigate these mechanisms, we focused on Charcot-Marie-Tooth disease (CMT) which is well known as the most common form of inherited peripheral neuropathy including pain symptoms. In this study, we examined the expression of CMT genes in L-OHP-induced peripheral neuropathy in comparison with PTX-induced peripheral neuropathy.**Methods:** L-OHP (4 mg/kg) or PTX (6 mg/kg) was administered intraperitoneally, on two consecutive days per week for 4 weeks. Peripheral neuropathy was measured by the von Frey test, mechanical allodynia, on day 0, 3, 10, 17, and 24. CMT genes, peripheral myelin protein 22 (Pmp22), myelin protein zero (Mpz) and mitofusin 2 (Mfn2) mRNA expression were analyzed in the spinal cord by qRT-PCR on day 3 and 24. **Results:** Both L-OHP and PTX induced mechanical allodynia from day 17 to 24. In addition, L-OHP reduced Pmp22 and Mpz mRNA expression, but not Mfn2 mRNA expression, on day 24. On the other hand, PTX reduced Mfn2 mRNA expression, but not Pmp22 or Mpz mRNA expression, on day 3 and 24. **Discussion:** Our results show that Pmp22 and Mpz mRNA decreased in L-OHP-induced mechanical allodynia, and Mfn2 decreased in PTX-induced mechanical allodynia. It has been known that Pmp22 and Mpz constitute myelin in the peripheral nervous system, and Mfn2 regulates axonal transport of mitochondria. Taken together, our finding suggests that L-OHP-induced peripheral neuropathy is caused by myelin degeneration, and PTX-induced peripheral neuropathy is caused by axonal degeneration.

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Poster

136. Mechanisms of Neurodegeneration I

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA training grant: T32DA007262

Methamphetamine Abuse Research Center: 1P50 DA018165

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Title: Trace amine-associated receptor 1 (TAAR1) modulates thermal and neurotoxic responses to MDMA and methamphetamine

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Abstract: The trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor (GPCR) that inhibits dopamine (DA) neuron firing when activated. Sensitivity to the effects of amphetamines is altered when TAAR1 is absent or non-functional. Two different TAAR1 mouse models were used to investigate thermal response to 3,4-methylenedioxymethamphetamine (MDMA): 1) mice selectively bred to voluntarily consume high amounts of methamphetamine (MA) (MAHDR) and possessing a *Taar1* allele that encodes a non-functional TAAR1 were compared to low consumers of MA (MALDR) expressing a functional TAAR1; and 2) *Taar1* genetic knockout (KO) mice lacking TAAR1 were compared to wildtype (WT) mice. Animals received 4 i.p. injections, 2 hr apart, of saline or MDMA (20 mg/kg) and temperature was measured *via* radio telemetry. Thirty min after injection, a significant hypothermic drop in body temperature occurred in MALDR and *Taar1*-WT mice receiving MDMA, while this response was significantly diminished in MAHDR and *Taar1*-KO mice. MAHDR/MALDR mice also received the same dosing regimen of methylone (25 mg/kg), a methcathinone lacking TAAR1 affinity, which elicited no difference in thermal response between MALDR and MAHDR mice. *Taar1*-WT and -KO mice were also administered a neurotoxic regimen of MA: 4 i.p. injections, 2 hr apart, of saline or MA (2.5, 5, or 10 mg/kg). Temperature data were recorded and striatal tissue collected 2 or 7 days later for analysis of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), as well as glial fibrillary acidic protein (GFAP) expression. MA elicited an acute hypothermic drop in body temperature in *Taar1*-WT mice that was more pronounced at the two lower doses of MA. This hypothermia was significantly attenuated in *Taar1*-KO mice by all MA doses. MA dose-dependently decreased DA and DOPAC levels 2 days following administration and DA levels were lower in *Taar1*-KO compared to -WT mice, regardless of treatment. Seven days later, DA levels were significantly decreased by MA 2.5 and 5 mg/kg in *Taar1*-KO compared to -WT mice, while DOPAC and HVA were lower in *Taar1*-KO compared to -WT mice, regardless of treatment. Two and 7 days later, GFAP expression was increased by all doses of MA, and significantly increased by MA 2.5 and 5 mg/kg in *Taar1*-KO compared to -WT mice. These results demonstrate TAAR1 activation is necessary for MDMA or MA-induced hypothermia. Additionally, absence of TAAR1 increases sensitivity to MA-induced neurotoxicity, indicating that activation of TAAR1 confers neuroprotection, potentially attributed to TAAR1-mediated acute hypothermia.**Acknowledgement**: David K. Grandy provided *Taar1* transgenic breeders.

Disclosures: **N. Miner:** None. **M.H. Baumann:** None. **T.J. Phillips-Richards:** None. **A.J. Janowsky:** None.

Poster

136. Mechanisms of Neurodegeneration I

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Title: Neurodegeneration of the inner retina and corneal nerve fiber morphology in experimentally diabetic rats

Authors: *A. J. BARBER[1,2], S. D. KIM[2], P. NGUYEN[2], B. BACCOUCHE[2,3], W.-W. WANG[2], J. M. SUNDSTROM[2]
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Abstract: Diabetes induces degeneration of the retina that includes vascular pathology and loss of the blood-retinal barrier, leading to macular edema and diabetic retinopathy. Recent clinical data using spectral domain optical coherence tomography (SD-OCT) suggest that the inner retina may degenerate earlier than the advent of gross vascular pathology. Other evidence using scanning confocal imaging suggests that corneal nerve fibers may also degenerate in diabetes. This study aimed to measure and compare retinal cell layer thickness, retinal cell death and corneal nerve fiber density in streptozotocin (STZ)-diabetic rats. Adult male Long-Evans rats were made diabetic by streptozotocin injection (STZ, 100 mg/kg, i.v., n=6) and housed with age-matched controls (n=6). Retinal morphology was measured by SD-OCT (Envisu 2210, Bioptigen) 9 weeks later. Rats were sacrificed after 10 weeks of diabetes and retinas were homogenized to assess apoptosis by a cell death ELISA. Corneas were dissected, labeled for β-tubulin and flat-mounted for confocal microscopy (Leica SP8). Images from 5 random 116.25 μm^2 regions were obtained. Corneal nerve fiber density (number/mm^2) and corneal nerve fiber length (mm/mm^2) were measured by image analysis using Neuron J. Statistical comparisons were made by two-tailed t-test with $p<0.05$ considered significant (Prism, Graphpad). Cell death was significantly elevated in retinas of STZ-diabetic rats compared to controls ($p<0.05$). SD-OCT revealed that the inner plexiform and inner nuclear layers were significantly thinner in the

STZ-diabetic rats compared to controls ($p<0.05$ and $p<0.01$ respectively), while the outer nuclear and photoreceptor layers were significantly thicker ($p<0.001$ and $p<0.05$ respectively). Morphological analysis of the corneal nerve fibers revealed no significant differences between the STZ-diabetic and control groups. Elevated retinal apoptosis and thinning of the inner plexiform and inner nuclear layers indicate diabetes-induced neurodegeneration of the inner retina with a potential loss of synaptic connectivity. Thickening of the outer nuclear and photoreceptor layers is most likely due to fluid accumulation caused by increased permeability of the blood-retinal barrier. This study found no significant effect of diabetes on corneal nerve fiber morphology, suggesting that these neurons do not significantly degenerate before the inner retina in STZ-diabetic rats. Taken together our data suggest that inner retinal degeneration and outer retinal swelling occur in parallel during the first 10 weeks of STZ-diabetes but are not accompanied by changes in corneal neuron morphology.

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Poster

136. Mechanisms of Neurodegeneration I

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

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Title: Effects of early life manganese exposure on markers of glutamatergic and dopaminergic neurotransmission in motor cortex

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Abstract: Motor impairments have been observed in children exposed to excess levels of manganese early in life, and chronic, pre-weaning manganese exposure in rats leads to fine

motor dysfunction. Developmental manganese exposure may also disrupt catecholaminergic signaling in striatum and prefrontal cortex, brain regions important for control of skilled motor function. The primary motor cortex (M1) also plays a role in regulating fine motor function, and in motor skill learning. Plasticity of M1 dendritic spines, the postsynaptic targets of most cortical excitatory synapses, is associated with skilled motor learning in rodents, and dopaminergic projections to M1 originating in the ventral tegmental area have been shown to contribute to motor skill learning. However, the extent to which early life manganese exposure alters excitatory synapse plasticity or dopaminergic inputs in M1, and how these changes relate to motor impairments, is not known. Our objective was to determine how early life manganese exposure impacts excitatory synapses and dopaminergic signaling markers within M1. Mice were orally exposed to manganese daily until weaning. Using transcranial *in vivo* two photon microscopy, we longitudinally imaged dendritic spines on M1 apical dendrites of control and manganese-exposed *Thy1*-YFP-H line mice, which express YFP in a sparse subset of cortical layer 5 (L5) pyramidal neurons. Adolescent manganese-exposed mice displayed decreased spine elimination and increased spine density on L5 apical dendrites in M1 compared to control littermates. In conjunction with spine alterations, mice exposed to manganese during early development also exhibited motor skill impairments. These results suggest that early life manganese exposure disrupts M1 dendritic spine plasticity, and that excitatory synapse perturbations may have an impact on the ability to execute fine motor tasks. Further analysis will determine whether the presynaptic components of excitatory synapses in M1 are altered in parallel with changes in postsynaptic spines, and how mesocortical dopaminergic signaling in M1 is impacted by early life manganese exposure.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.06/Y1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Lipid signaling during neuronal degeneration in KA-treated mice

Authors: *F. CHALI[1], S. MARTY[2], G. MILIOR[2], M. MORIN-BRUREAU[2], C. LE DUIGOU[2], E. SAVARY[2], R. MILES[2]
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Abstract: Cholesterol and lipid homeostasis is dysregulated in several neurodegenerative diseases (Yadav and Tiwari 2014; Gaschler and Stockwell 2016). Similarly some lipids are altered after excitotoxicity injuries that lead to temporal lobe epilepsy (Kim et al 2009; Xu et al

2008; Takei et al 2012; Heverin et al 2012). However, the mechanisms underlying the pathogenic effects induced by changes in lipid homeostasis are unclear. We have shown that increasing neuronal free cholesterol, by suppressing the extruding enzyme cholesterol 24-hydroxylase, induces neuronal death and eventually epileptiform activity in the hippocampus (Chali et al 2015). Here we examined changes in sterols, lipids, and transcripts that control their homeostasis during the neuronal death induced by focal kainic acid (KA) injection in the CA1 region of the hippocampus. At 1-2 days after KA treatment, lipid droplets were detected in microglia. Filipin staining revealed punctate deposits of free cholesterol in neuronal somata at 2-4 days. We correlated these changes with EM data on damage to cellular organelles and transcriptomic changes from RNA-seq. Our data highlight the extent and role of lipid dysregulation in excitotoxic neuronal death.

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Poster

136. Mechanisms of Neurodegeneration I

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: AG023084 to B.V.Z.

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Title: Neuronal-specific PICALM deficiency causes cognitive impairment and brain atrophy

Authors: *D. LAZIC[1,2], A. MONTAGNE[1], Z. ZHAO[1], T. MAEDA[3], M. MAEDA[3], B. V. ZLOKOVIC[1]
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Abstract: *PICALM*, a gene encoding phosphatidylinositol-binding clathrin assembly protein, is a highly-validated genetic risk factor for Alzheimer's disease (AD). Besides its well-known role in regulating the intracellular trafficking of endocytic vesicles, studies in *Picalm+/-* mice revealed that PICALM is involved in the transcytotic clearance of amyloid-β across the blood-brain barrier. On the other hand, genetic analyses and magnetic resonance imaging (MRI) in humans suggested the positive correlation between protective *Picalm* allele and higher hippocampal volume as well as increased entorhinal cortical thickness. Furthermore, studies had shown that in developing neurons PICALM assists fusion of synaptic vesicles with presynaptic membranes and regulates the size and density of synaptic vesicles, suggesting its role in synaptic transmission.

Because PICALM plays essential roles in regulating axonal growth and turnover of synaptic vesicles and receptors, a complete deletion of PICALM from neurons can be detrimental to neuronal homeostasis. In order to examine the role of PICALM in neuronal health and cognitive performances in adult mice, we generated tamoxifen-inducible neuron-specific PICALM knockout line (*Picalm$^{lox/lox}$; Camk2a-CreER*). Four weeks after tamoxifen administration, *Picalm$^{lox/lox}$; Camk2a-CreER* mice showed cognitive impairment as demonstrated with novel object location/recognition and fear conditioning behavioral paradigms. Volumetric studies using 11.7T MRI scanner and immunohistochemistry on neuronal markers revealed that *Picalm$^{lox/lox}$; Camk2a-CreER* mice exhibit brain atrophy, most prominent in the hippocampus. After bilateral intrahippocampal injections of amyloid-β oligomers, we found more susceptibility to neuronal death compared to vehicle injected *Picalm$^{lox/lox}$; Camk2a-CreER* mice. Studies in primary neuronal culture using *Picalm$^{-/-}$* pups confirmed *in vivo* findings on increased susceptibility of PICALM-lacking neurons to insults such as amyloid-β. Altogether, our data suggest that neuronal PICALM plays an important role in cognition and neuronal health.

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Poster

136. Mechanisms of Neurodegeneration I

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Program#/Poster#: 136.08/Y3

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Overexpression of sigma-1 receptor rescues G4C2 RNA repeats-mediated defect in the nucleocytoplasmic transport of Ran GTPase: Implication in ALS

Authors: *P.-T. LEE[1], T.-P. SU[2]
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Abstract: The GGGGCC (G_4C_2) hexanucleotide repeat expansions within *chromosome 9 open reading frame 72 (C9ORF72)* have been characterized as the most common genetic abnormality in amyotrophic lateral sclerosis (ALS). Expanded G_4C_2 repeats led to the mislocalization of nuclear pore complex (NPC) component protein nucleoporins in *C9ORF72* motor cortex as well as the nucleocytoplasmic transport defect of Ran GTPase in patient-derived induced pluripotent stem cells (iPSCs) neurons. G_4C_2 repeat expansions can directly interact with Ran GTPase-activating protein 1 (RanGAP1), leading to the nucleocytoplasmic transport disruption by impairing the nucleus/cytosol (N/C) gradient of Ran GTPase. Therefore, understanding how G_4C_2 repeat expansions work in the NPC is important for treatment of ALS/FTD patients. Our previous results showed that sigma-1 receptors (Sig-1Rs) bind to FG-repeat NPC nucleoporins

and increase their half-life. Immmunoprecipitation assay and fluorescence confocal microscopy revealed that Sig-1Rs interact with RanGAP1 in the nuclear envelopes. The biotin labeled G_4C_2 RNA repeats interacted with the recombinant glutathione S-transferase (GST)-tagged Sig-1Rs proteins in the GST pull-down assay. We found here that by using the RNA fluorescence in situ hybridization (RNA-FISH) assay that Sig-1Rs partly colocalize with Cy3-labeled G_4C_2 RNA repeats in the perinuclear region. Interestingly, the overexpresson of Sig-1Rs can attenuate the defect of N/C ratio of Ran GTPase caused by the G_4C_2 repeats. Our results propose a novel mechanism whereby increasing the level of Sig-1Rs in the NPC by pharmacological or cellular biological means may represent a novel avenue for treating the *C9ORF72* G4C2-repeats subtype of ALS (This work was supported by IRP/NIDA/NIH/DHHS)

Disclosures: P. Lee: None. **T. Su:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

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Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS079172

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Title: The role of tubulin post-translational modifications in HIV gp120-mediated neurotoxicity

Authors: *E. WENZEL[1], F. TARABELLI[2], I. MOCCHETTI[1], V. AVDOSHINA[1]
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Abstract: Despite successful antiretroviral drug therapy, a subset of Human Immunodeficiency Virus-1 (HIV) positive individuals still display synapto-dendritic simplifications and functional cognitive impairments. These symptoms are referred to as HIV-associated neurocognitive disorders (HAND). Considerable experimental evidence indicates that HIV proteins, including the envelope protein gp120, can cause neurological damage to a similar extent as the full virus. However, the full mechanism of gp120-mediated neurotoxicity is still unknown. We have recently established that internalized gp120 binds with high affinity to class III β-tubulin, a component of neuronal microtubules, through a conserved α-helical motif. Therefore, we hypothesize that gp120 impairs axonal transport of organelles and essential nutrients for neurons by altering microtubules. To test this hypothesis, we first investigated the neuroprotective effect of a small peptide, “Helix-A”, which displaces gp120 from binding to tubulin. Helix-A prevented gp120-mediated cell death of primary rat cortical neurons as measured by Hoechst/propidium iodide staining. We next determined the ability of gp120 to cause tubulin deacetylation, a post-

translational modification which has previously been demonstrated to impair microtubule-mediated axonal transport. Exposure of cortical neurons to gp120 elicited a time-dependent decrease in tubulin acetylation that was reversed by Helix-A. We then used a pharmacological approach to prevent gp120-mediated tubulin deacetylation. Tubulin deacetylation is regulated by HDAC6 and we used tubacin, a potent and selective HDAC6 inhibitor, to confirm whether this post-translational modification of tubulin underlies the neurotoxic effect of gp120. We have demonstrated that tubacin prevents gp120-meditaed deacetylation of tubulin and may be an additional potential neuroprotective treatment for gp120-mediated neuronal loss. Overall, our data suggest that gp120 decreases tubulin acetylation and impairs microtubule-dependent transport. Our novel work indicates that gp120-mediated neurotoxicity, and therefore HAND, may be a disease of the neuronal cytoskeleton.

Disclosures: **E. Wenzel:** None. **F. Tarabelli:** None. **I. Mocchetti:** None. **V. Avdoshina:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.10/Y5

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Intracranial vascular calcification in an autopsy case of pseudopseudohypoparathyroidism

Authors: *T. IWASE[1], M. YOSHIDA[2], Y. HASHIZUME[3], I. YAZAWA[4]
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Abstract: Pseudopseudohypoparathyroidism (PPHP) patients have features of Albright osteodystrophy without renal resistance to parathyroid hormone. They are also known to have intracranial calcification in the bilateral basal ganglia and cerebellar dentate nuclei, refferred to as Fahr's syndrome. In most cases, brain calcifications were detected by computed tomography. In this study, we investigated the exact distribution and extent of the calcifications, and their impact on the brain tissue. Brain and spinal cord from an autopsied PPHP patient were neuropathologically investigated. The formalin-fixed paraffin-embedded sections stained with hematoxylin-eosin, Klüver-Barrera, Holzer, von Kossa, Berlin blue and immunostainings for GFAP, neurofilament, α-SMA, and CD34 were used. Massive calcification within the vessel walls and capillaries were revealed in the basal ganglia and cerebellar dentate nuclei. The vascular calcification was not confined to subcortical gray matter but continuously spread over the surrounding white matter into the depths of cortical sulci and subarachnoid space. The calcification was closely related to the gray and white matter lesions with gliosis and

demyelination. The extensive white matter lesions may be a cause of neuropsychiatric symptoms in PPHP manifesting Fahr's syndrome.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.11/Y6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Evaluation of mouse strain differences in esterase and nerve agent-induced toxicity

Authors: *L. M. MATSON, J. CHANDLER, C. ARDINGER, C. CADIEUX, H. CRAIG, J. KOENIG, H. MCCARREN, Z. CANTER, H. HOARD-FRUCHEY, T.-M. SHIH, E. JOHNSON, D. CERASOLI, J. MCDONOUGH
US Army Med. Res. Inst. of Chem. Def, Aberdeen Proving Ground, MD

Abstract: Genetic background influences susceptibility to the toxicity induced by nerve agents (NA). Our strategy is to identify sensitive and resistant mouse strains to discover pathways involved in NA-induced toxicity. In Experiment 1, we measured esterase levels to identify if pharmacokinetic factors contribute to strain toxicity differences. Blood and cortex samples were collected from males and females of 10 inbred mouse strains. Plasma carboxylesterase (CE), plasma butyrylcholinesterase (BChE), and red blood cell (RBC) and cortex acetylcholinesterase (AChE) activity levels were measured using modified Ellman assays. We performed univariate analysis of variance (ANOVA) to identify if there were strain differences in esterase activity levels. There was a significant strain difference in cortex AChE activity levels ($p < .05$), which appeared to be driven by a trend for activity differences between DBA and C57 mice ($p = .065$). There was a significant strain difference in RBC AChE ($p < .001$), which was driven by the C57 strain having a higher activity than all other strains (ps $< .01$). There were no differences in CE or BChE activity levels across the strains. To identify novel methods underlying toxicity differences, the C57BL6/J and C3H/HeJ strains were removed from subsequent analyses. In Experiment 2, a stagewise, adaptive dose procedure was used to measure median lethal dose (MLD) levels in 8 mouse strains. MLD determinations are ongoing, although initial data suggest variation in MLD levels across the strains. These data will inform future molecular analyses of pathways involved in resistance or sensitivity to NA-induced toxicity.The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. The views expressed in this abstract are those of the author(s) and do not reflect the official policy of the Department of Army, Department of

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Poster

136. Mechanisms of Neurodegeneration I

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.12/Y7

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Aim for the Top University Plan, Ministry of Education, Taiwan

Title: Soluble epoxide hydrolase inhibition attenuates excitotoxicity via upregulating glutamate transporter in rat brain

Authors: *Y.-M. KUO[1,3], P.-C. HSU[2], Y.-Y. HU[2], Y.-H. LEE[2]
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Abstract: Soluble epoxide hydroxylase (sEH) is a dual activity enzyme with the C-terminal hydrolase activity mediating metabolic degradation of epoxyeicosatrienoic acids (EETs). The neuroprotective effect of sEH inhibitor was attributed to accumulation of a prosurvival 14,15-EET and its anti-inflammatory effect. Pharmacologic inhibition and genetic deletion of sEH have been shown to ameliorate the neural injury induced by experimental stroke, modulates epilepsy development and pain signaling. Yet, recent study revealed that sEH inhibitor can facilitate excitatory postsynaptic potential in rat hippocampal slice, raising a question on how this action mechanism would affect glutamate-induced excitotoxicity. In the present study, we used primary rat cortical neurons to investigate the effect of a C-terminal sEH inhibitor 12-(3-adamantan-1-yl-ureido)-dodecanoic acid (AUDA) and 14,15-EET on the NMDA-induced excitotoxicity *in vitro*. *EPHX2* gene expression was enhanced under NMDA excitotoxicity. While knockdown of *EPHX2* and 14,15-EET treatment can attenuate NMDA excitotoxicity, sEH inhibitor AUDA surprisingly enhanced NMDA-induced excitotoxicity with the increase in LDH release and TUENL stain. Thus, AUDA and 14,15-EET seem to opposingly affect NMDA excitotoxicity. Of note, AUDA attenuated NMDA-reduced EET and partial restored NMDA-decreased neurite density. Therefore we used rat i.c.v KA model to investigate the AUDA effect on the excitotoxicity *in vivo*. AUDA did not reduced seizure score after i.c.v KA injection. However

IHC showed AUDA selectively protects against KA-reduced NeuN positive neurons and MAP-2 neurite in dentate gyrus but not in CA3 of hippocampus. TUNEL stain showed that AUDA significantly decreased KA-induced apoptosis in CA3. These protective effects of AUDA correlate with its upregulation of the glutamate transporter EAAT2 enriched in astrocytes, which was depleted by KA in pyramidal cell layer in CA3 and partially restored by AUDA. We further used rat glia-neuronal mix-culture and found that both AUDA and 14,15-EET can enhance EAAT2, also further enhanced NMDA-induced EAAT2 expression. These results revealed that the neuroprotective effect of sEH inhibition on excitotoxicity-induced brain injury is attributed to its upregulation of astrocytic EAAT2 to prevent glutamate overflow, which counterbalances its excitotoxicity-enhancing effect to neurons.
(Supported by Aim for the Top University Plan, Ministry of Education, Taiwan)

Disclosures: **Y. Kuo:** None. **P. Hsu:** None. **Y. Hu:** None. **Y. Lee:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.13/Y8

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Modifying chondroitin sulfation enhances retinal ganglion cell axon regeneration in the mouse optic nerve

Authors: *C. S. PEARSON[1], K. R. MARTIN[2], H. M. GELLER[1]
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Abstract: Retinal ganglion cell (RGC) axon regeneration is not spontaneous, but can be induced by inflammation, genetic manipulation, or other stimuli. However, regrowth to central targets is limited in part due to the inhibitory extracellular environment of the optic nerve. We characterized the spatial and temporal expression of inhibitory chondroitin sulfate proteoglycans (CSPGs) after optic nerve crush (ONC) in mice, with the aim of modifying CSPGs to enhance RGC axon regeneration in vivo. CSPG expression was assessed by immunohistochemistry 1, 3, 5, 7, 14, and 21 days post crush (dpc) using antibodies against CSPGs, including a specific sulfated epitope (4S) known to be inhibitory to axon growth in vitro, and markers for reactive astrocytes (GFAP) and activated microglia (Iba1) (n=3 per group). Elevation of CSPGs, including the 4S epitope, was observed at the lesion site from 3 dpc, peaking at 7d and remaining detectable until 21 dpc. Reactive astrocytes withdrew from the lesion site, creating a GFAP-negative zone filled with Iba1-positive microglia and macrophages. CSPGs occupied spaces between Iba1-positive cells, alongside RGC axons, suggesting that axons must travel through CSPG-rich regions while growing past the lesion. Next, to assess the effects of CSPGs on RGC

axon regeneration, mice received ONC, and at 3 dpc were administered an intravitreal injection of zymosan and a 1 mm^3 gelfoam scaffold soaked in either chondroitinase ABC (ChABC), arylsulfatase B (ARSB), or a control buffer, applied directly to the injured optic nerve (n=8 per condition). The growth associated protein GAP-43 was used to visualize regenerating RGC axons in cryosections obtained 14 dpc. Axon regeneration was quantified by counting the number of GAP-43+ axons crossing various distance benchmarks from 0.5 to 1.5 mm distal to the lesion site, measuring the nerve width, and calculating the total number of regenerating axons per nerve. The results showed that zymosan effectively stimulates low levels of RGC axon regeneration, and that delivery of ChABC and ARSB increased the number and distance of regenerating axons. Therefore, inactivating CSPGs with ChABC and ARSB enhances intrinsically-stimulated RGC axon regeneration, demonstrating that CSPGs at the lesion site inhibit growing axons and that modifying the extracellular environment may improve intrinsic regenerative therapies.

Disclosures: C.S. Pearson: None. **K.R. Martin:** None. **H.M. Geller:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.14/DP04/Y9 (Dynamic Poster)

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: 5P01AI073693-08

Title: A two-part model of neuropsychiatric systemic lupus erythematosus involving acute autoantibody mediated neuronal death and chronic pruning by microglia

Authors: *J. NESTOR[1,2], Y. ARINUMA[3], C. KOWAL[1], T. S. HUERTA[1], P. T. HUERTA[1,2], T. R. HAMMOND[4], B. A. STEVENS[4,5], B. T. VOLPE[1,2], B. DIAMOND[1,2]
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Abstract: Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is seen in a subset of SLE patients, and involves a variety of symptoms, including cognitive dysfunction. Autoantibodies are a hallmark of SLE and we have shown in a mouse model that these antibodies can attack the brain in NPSLE. Our model utilizes immunization with DWEYS peptide, a sequence found on the N-methyl-D-aspartate receptor (NMDAR), which stimulates the production of anti-DWEYS antibodies, cross-reactive to dsDNA. These autoantibodies are present in 30% of SLE patients. They are restricted from the brain unless the blood brain barrier (BBB) is breached. When lipopolysaccharide (LPS) disrupts the BBB we see both acute neuronal loss and chronic dendritic

loss in surviving neurons localized to the hippocampus. This study looks to understand the mechanisms underlying both the acute and chronic processes.
Our model allows for immunization and LPS administration in a variety of genetic knockout strains of mice including mice with deletion of the GluN2A or GluN2B subunit of the NMDAR and the complement protein C1q. Acute neuronal loss occurs in DWEYS-immunized wildtype and GluN2B knockout mice, but not in the GluN2A knockout mice, suggesting excitotoxic neuronal death is mediated through the GluN2A subunit of the NMDAR. In wildtype mice we observe an increase in microglial activation in DWEYS-immunized mice compared to control-immunized mice. Furthermore, in C1q knockout mice, no change in dendritic complexity or spine density was seen between control and DWEYS-immunized mice. Electrophysiologic studies show DWEYS-immunized wildtype mice have expanded placefields, whereas no impairment in placefields was seen in C1q knockout mice.
This study suggests a two-part model of NPSLE that acutely involves neuronal excitotoxic death mediated through the GluN2A subunit of the NMDAR, and chronically involves dendritic and spine loss due to C1q and activated microglia. This suggests two potential temporal targets for the development of therapeutics for NPSLE.

Disclosures: **J. Nestor:** None. **Y. Arinuma:** None. **C. Kowal:** None. **T.S. Huerta:** None. **P.T. Huerta:** None. **T.R. Hammond:** None. **B.A. Stevens:** None. **B.T. Volpe:** None. **B. Diamond:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.15/Y10

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: The effects of an active core sequence of beta amyloid on ER stress and the MAPK linked toxicity pathway

Authors: *K. FOREST[1,2], R. M. TAKETA[1,2], R. A. NICHOLS[1,2]
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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory decline and loss of cognitive functions. AD is histologically characterized by the pathological aggregation of beta amyloid (Aβ) and tau neurofibrillary tangles. Monomeric soluble Aβ can switch from helicoidal to β-sheet conformation, promoting its assembly into toxic oligomers. These oligomers have been reported to induce neuronal death and synaptic transmission impairments. However, there is now considerable evidence that in normal healthy brains, soluble oligomeric Aβ functions as a neuromodulator. Recently, our laboratory has shown that at low concentrations (pM-nM) a naturally produced N-terminal Aβ fragment (N-Aβ

fragment) is nearly twice as effective as full-length Aβ as a neuromodulator, stimulating receptor-linked increases in Ca^{2+}, enhancing long-term potentiation (LTP) and enhancing contextual fear conditioning. In addition, we have shown that N-Aβ fragment protects against $A\beta_{42}$-induced neurotoxicity. We further identified a hexapeptide core sequence within N-Aβ fragment, YEVHHQ (N-Aβcore), which is found to be equally as effective in Ca^{2+} signaling and is also neuroprotective against $A\beta_{42}$-induced oxidative stress and neuronal death. To further elucidate the pathways of N-Aβcore on neuroprotection, we examined changes on pPERK for ER stress as well as various kinases in the MAPK pathway that has been linked with $A\beta_{42}$-induced toxicity. Of these kinases, a few have been implicated in learning and memory upon NMDAR activation.
We investigated the role of the N-$A\beta_{core}$ against $A\beta_{42}$-induced MAPK and PERK activation by examining the extent of pERK, pJNK, p38, and pPERK after treatment with the N-$A\beta_{core}$ in the presence of $A\beta_{42}$ on neuronal cultures. In addition, we assessed the neuroprotective action of N-$A\beta_{core}$ on synaptic plasticity in rodent hippocampal slice LTP.
Elucidating the molecular pathway of the N-$A\beta_{core}$ provides a better understanding of its neuroprotective mechanism and its role at the synapses in the context of accumulating Aβ in AD. The neuroprotective action of the N-$A\beta_{core}$ suggests the possibility of using this core sequence as a scaffold for optimization of a potential biologic for protection against Aβ -induced toxicity.
Funding: NIGMS (P20GM103466) and the UH Foundation

Disclosures: K. Forest: None. **R.M. Taketa:** None. **R.A. Nichols:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.16/Y11

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS-R15NS095317

TWU Research Enhancement Program

Title: Variations in the metabolism and aggregation of TDP43 fragments

Authors: *Y. T. KASU, C. S. BROWER
Biol., Texas Woman's Univ., Denton, TX

Abstract: Despite uncertainty surrounding the exact molecular cause of neurodegeneration, a defining feature is the accumulation and aggregation of neuronal protein fragments resulting from an increase in their production, or a decrease in their removal. A variety of C-terminal fragments of the TAR DNA-binding protein-43 (TDP43) have been found as major components

of intracellular aggregates associated with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar dementia (FTLD). Due to alternative cleavage sites within TDP43, the resulting C-terminal fragments contain distinct N-termini. The overall goal of this research is to determine the toxicity of C-terminal TDP43 fragments and to understand how they are metabolized. Previously, we found that specific ALS-associated fragments of human TDP43 accumulate in the absence of the N-end rule pathway of the ubiquitin proteasome system. Here, we found that TDP43 C-terminal fragments can vary in their dependency on the N-end rule for degradation and that they differ in their aggregation propensities in Neuro2a cells. We are also examining the relative toxicity of C-terminal TDP43 fragments in cells as well as in yeast and in mice. These studies will help to determine if aggregation-prone neuronal protein fragments play a causative role in disease; and ultimately may help in developing therapeutic strategies for neurodegeneration.

Disclosures: Y.T. Kasu: None. **C.S. Brower:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.17/Y12

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Smokeless tobacco: A threat for neuronal cell death modulating AKT/GSK3β signalling axis

Authors: *S. BISWAS[1], H. DAS[2], U. DAS[1], K. MANNA[1], A. SENGUPTA[1], S. C. BISWAS[2], R. S. DEY[3], S. DEY[1]
[1]PHYSIOLOGY, UNIVERSITY OF CALCUTTA, KOLKATA, India; [2]Cell Biol. and Physiol. Div., CSIR-Indian Inst. of Chem. Biol., Kolkata, India; [3]Dept. of Food and Nutr., Barrackpore Rastraguru Surendranath Col., Kolkata, India

Abstract: Smokeless tobacco (SLT), the form of tobacco which is not consumed by smoking also known as “chewing tobacco” has become a huge disease burden globally. SLT leads to several counts of detrimental effects on human health. It is being used by a huge population across the globe as a form of addiction. Prolonged habit of SLT may cause oral injury and inflammation. Untreated events eventually lead to carcinogenic developments. SLT is assorted with betel leaves, areca nut, lime, catechu, toxic chemicals like polycyclic aromatic hydrocarbons, nitrate, nitrite, nicotine, acrolein and chemicals such as crotonaldehyde, substantial amounts of formaldehyde and acetaldehyde. It is available in common Indian market as “*gutkha*”. It is known that some of the active components of SLT cross blood brain barrier through nicotinergic and some other receptors. In this study the major interest is to observe whether SLT could be a causative factor for neuronal cell death and to explore the probable

mechanism of action *in vitro*. We studied the effects of graded doses of water soluble lyophilised SLT (0.5-10 mg/ml) on PC12 (rat pheochromocytoma) and SH-SY5Y (human neuroblastoma) cell line after differentiation. We measured cell viability, total ROS generation, mitochondrial ROS generation, mitochondrial trans-membrane potential (MMP) and health. One specific dose of SLT with 50% cell death was chosen for further time kinetics study. Increased level of cleaved PARP and pH2AX started appearing from 4h indicating evidence for DNA damage, increased level of pro-apoptotic proteins (Bax, t-Bid) and decreased level of anti-apoptotic proteins (Bcl-2, Bcl-XL) were also observed with increasing time. Increased expression of caspase-cascade of intrinsic apoptotic pathway (caspase -9, -7, -3) was observed from 4h time point onwards. Cytochrome-*c* release was also observed with escalated doses of SLT for 24h of treatment. To understand the mechanism of cell death PI3-K/AKT pathway was studied. It was observed that there was decreased level of expression for pAKT (Thr 308) and pGSK3β (Ser 9) after 24 h of SLT treatment which are the signatures of survival pathway. Taken together current results proposed that SLT induced neuronal death via production of ROS, alteration of MMP, mitochondrial morphology, activation of caspase-cascade, apoptotic proteins and inactivation of the pAKT/GSK3β signalling pathway. This is perhaps the first report conferring SLT mediated differentiated neuronal cell death.

Disclosures: S. Biswas: None. **H. Das:** None. **U. Das:** None. **K. Manna:** None. **A. Sengupta:** None. **S.C. Biswas:** None. **R.S. Dey:** None. **S. Dey:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.18/Y13

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Title: Altered spine dynamics and dendritic damage in a mouse model of neuroprotective thermal torpor

Authors: *J. BRILL, R. H. CUDMORE, D. J. LINDEN
Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Hibernating animals, e.g. some ground squirrels and hamsters, experience prolonged periods of low basal body temperature, associated with a reversible decrease in dendritic spine density. In non-hibernating animals, including humans, cooling is used to reduce neuronal damage after ischemia, and during certain types of surgery such as aortic arch or aneurism repair. However, the effects of this transient cooling on neuronal fine structure are poorly understood. To investigate how a reduction in body temperature affects dendritic spine dynamics, we implanted cranial windows above the somatosensory cortex in Thy1-GFP-M mice (n=6), which sparsely express GFP in layer 5 cortical pyramidal cells. Images of the apical dendrites in layer I

were then acquired using a 2-photon microscope.
A state of torpor - reduced metabolic rate which causes the body temperature to drift towards ambient temperature - was induced in adult mice by injecting AMP (1 mg/kg, IP). At an ambient temperature of 15°C, we achieved torpor durations of >8 hours with minimal mortality. Control images were obtained during a 10 day period to measure baseline spine dynamics. Animals were then imaged one and eight hours after torpor induction, and then at various intervals for up to eight weeks. We found that the density of filopodia-like, long, thin processes decreased during torpor (from 0.211+/-0.022 to 0.047 +/- 0.016 spines/10µm, $p<0.001$) and recovered within one week. There was no significant change in the density of other types of spines (1.619+/-0.166 vs. 1.514+/-0.182 spines/10µm). Turnover rates for non-filopodia-like spines increased transiently within 24 hours of torpor (3.32+/-0.66 fold increase in turnover rate, $p<0.05$), and returned to baseline values at later time points. Both spine addition and spine elimination were affected to a similar extent. Cooling also produced damage to dendrites, with prominent swellings and some shortening of dendritic tips, both of which recovered within 2-3 weeks. We ranked animals according to the severity of dendritic damage and to the extent of changes in spine dynamics. There was no significant correlation between spine dynamics and dendritic damage, suggesting that these are independent phenomena.

Disclosures: J. Brill: None. **R.H. Cudmore:** None. **D.J. Linden:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.19/Y14

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Intramural Research Program of the NIH, National Institute on Aging

NIA Research and Development Contract N01-AG-3-2124

NIA Research and Development Contract HHSN-260-2004-00012C

Title: Metabolic syndrome is related to accelerated amyloid accumulation and cortical thinning in the older brain

Authors: *L. L. BEASON-HELD[1], G. GOMEZ[1], N. DIPROSPERO[1], M. BILGEL[1], Y. AN[1], A. SHAFER[1], D. F. WONG[2], S. STUDENSKI[1], S. M. RESNICK[1]
[1]NIA, NIH, Baltimore, MD; [2]Radiology, Johns Hopkins Med. Insts., Baltimore, MD

Abstract: Metabolic Syndrome (MetS) is a disorder characterized by abdominal obesity, elevated triglycerides, low HDL cholesterol, elevated blood glucose, and high blood pressure. MetS is highly prevalent in older individuals, affecting approximately 50% of those over the age

of 60. A growing body of evidence supports a link between MetS and increased risk of Alzheimer's disease (AD), yet the brain basis of this relationship is unclear. We used data from participants in the Baltimore Longitudinal Study of Aging (BLSA) to explore the relationship between MetS and two brain measures associated with AD: cerebral amyloid accumulation and neocortical thinning. 166 participants (mean age at baseline=76.7) received annual 11C-Pittsburgh compound B (PiB) dynamic positron emission tomography (PET) scans to measure cerebral amyloid (Aβ) burden over an average of 2.7 years. 84 were MetS positive at baseline. Global cerebral amyloid status (positivity) and longitudinal regional change of amyloid accumulation were assessed. MetS was not associated with overall amyloid positivity, but the syndrome was associated with accelerated Aβ accumulation over time in superior parietal and precuneus regions in individuals with preexisting cerebral amyloid levels. Another 110 participants (mean age at baseline=69.9) underwent annual 1.5T MRI SPGR scans to measure cortical thickness over an interval of 7.2 years. 39 participants were MetS positive at baseline. MetS was associated with accelerated thinning in frontal, temporal and cingulate regions of the brain over time. These results suggest that MetS is associated with accelerated changes in neuropathology in areas of early amyloid accumulation in AD, and with structural changes in regions involved in higher-order cognitive processes. Together, the findings provide a link between MetS and brain changes associated with the onset of cognitive impairment and dementia in older individuals.

Disclosures: L.L. Beason-Held: None. **G. Gomez:** None. **N. DiProspero:** None. **M. Bilgel:** None. **Y. An:** None. **A. Shafer:** None. **D.F. Wong:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Avid Pharmaceuticals. **S. Studenski:** None. **S.M. Resnick:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.20/Y15

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS065808

Title: Dynamics of extracellular vesicle release in the CNS of the Twitcher mouse model of Krabbe Disease

Authors: *C. R. REITER[1], G. SCESA[2], A. KWAK[2], D. WOZNIAK[3], I. GIVOGRI[2], E. BONGARZONE[2]
[1]Med. Scientist Training Program, [2]Anat. and Cell Biol., Univ. of Illinois At Chicago, Chicago, IL; [3]Aurora Univ., Aurora, IL

Abstract: Krabbe Disease, also known as Globoid Cell Leukodystrophy, is a monogenetic lysosomal storage disorder caused by mutations in the gene encoding the enzyme galactosylceramidase (GALC). The loss of GALC enzymatic activity causes accumulation of a toxic sphingolipid, galactosylsphingosine (psychosine). Accumulation of psychosine has long been hypothesized to drive the observed pathology in Krabbe patients, including oligodendrocyte and Schwann cell cytotoxicity, astrogliosis, microglial activation and the presence of abnormal globoid cells throughout demyelinating white matter. Extracellular vesicles (EVs) are secreted by all mammalian cells, and are believed to facilitate communication between cells in development, homeostasis and pathologic states. EVs have the capacity to carry proteins, lipids, and nucleic acids, either intraluminally or on their membrane, lending them the potential to provide a vast array of communication signals. Recently, EVs have been established as valuable biomarkers found in biologic fluids of patients in various disease states. We have found EVs with elevated levels of psychosine in the Twitcher (Twi) model of Krabbe disease, and further characterized these populations by size and quantity. We hypothesize that extracellular vesicles contribute to the observed pathology in Krabbe Disease by one of two mechanisms; cells produce psychosine-laden EVs to preserve individual cell survival by unloading excess lipid, and/or induce pathology in distant cells through the spread of psychosine toxicity. To test these hypotheses, we wanted to see if we could reduce extracellular vesicle release, and observe how this affects the Twi phenotype and disease progression. We administered a treatment regimen of a Sphingomyelinase 2 inhibitor (GW4869), which has been demonstrated to reduce extracellular vesicle release. The inhibitor or vehicle was injected intraperitoneally every other day from postnatal day (P) 10 until P20 or P40. During the treatment period, mice were scored on weight, wire-hang, tremor, and locomotion to track disease progression. Vesicle populations were then isolated from Twi and wildtype brains using a stepwise sucrose gradient. EV populations are enriched in the brains of the Twitcher mouse model of Krabbe disease, and these vesicles are laden with psychosine. The inhibition of Sphingomyelinase 2 induced an earlier onset of the Twi phenotype, but did not change mouse survival. Of note, grip strength as a measurement of peripheral nervous system involvement, was preserved to a greater extent in our treated Twi mice. These findings highlight the contributions of vesicles to Twitcher disease pathology.

Disclosures: C.R. Reiter: None. **G. Scesa:** None. **A. Kwak:** None. **D. Wozniak:** None. **I. Givogri:** None. **E. Bongarzone:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.21/Y16

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NIDCD 1R01DC012829

Title: Inflammation of the taste system: Cyclophosphamide and Amifostine

Authors: A. ALI SARKAR, D. ALLYN, *E. R. DELAY
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Abstract: Chemotherapeutics are used extensively to treat cancer patients, and often induce adverse effects, including taste dysfunctions. Disturbances in taste are detrimental to the overall well-being of cancer patients, causing malnutrition and weight loss that aggravate their condition even further. To improve the quality of lives of these patients, it is important to address their taste-related concerns. Our research is studying molecular, cellular and behavioral aspects of the gustatory system affected by chemotherapy drugs such as cyclophosphamide (CYP). CYP is a pro-drug and once it is metabolized by the P450 enzyme complex, its primary metabolite functions as an alkylating agent. This research is examining potential drug-induced inflammation and changes in taste progenitor cell populations involved in taste cell renewal as factors underlying taste related changes. Previous research using TUNEL assay suggests CYP-induced cell loss in taste buds and non-taste epithelium of the tongue peaks about 8 hours after CYP administration (75 mg/kg, IP) and abates after 18-24 hours. In this study, Ki67 labelling indicated that CYP reduced the number of proliferating cells within 24 hour of injection. Fluorescent labelling indicated there is an increase in the expression of the cytokine TNF-alpha within the first 24 hours after CYP injection. Pretreatment with Amifostine (100 mg/kg, SC), a cytoprotective agent, appeared to protect taste cells by negating CYP-induced effects on proliferation and inflammation.

Disclosures: A. Ali Sarkar: None. **D. Allyn:** None. **E.R. Delay:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

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Program#/Poster#: 136.22/Y17

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R01DC012829

UVM SURF Grant Brennan Award

UVM APLE GRANT

Title: Differential cyclophosphamide induced disruptions of salt taste preference and detection

Authors: *B. C. JEWKES[1], M. G. GOMELLA[2], E. R. DELAY[3]
[1]Neurosci., Univ. of Vermont, South Burlington, VT; [3]Dept. of Biol., [2]Univ. of Vermont, Burlington, VT

Abstract: Chemotherapy is one of the most common cancer treatments, however altered taste is one of the most prevalent side effects, disturbing quality of life (Bernhardson et al., J Pain Symptom Manage, 2008). To investigate some of these disruptions on salt taste, two experiments were performed in a murine model evaluating alterations to appetitive qualities and detection thresholds of NaCl. Previous work in our lab (Muhkerjee & Delay, Neuroscience, 2011) found that the chemotherapy drug, cyclophosphamide (CYP), causes a two-phased disturbance in taste epithelium. The first phase is from initial cytotoxic damage triggering apoptotic pathways, whereas the second disruption is caused by depletion of progenitor cells that normally replace taste cells after they reach the end of their life span. We hypothesized IP injections of CYP would disrupt salt taste near days 2-4 post treatment (cytotoxic cell death), 8-11 and 20-26 in line with proposed half-lives of Types I, II and III taste sensory cells (Perea-Martinez et al., PLoS ONE, 2013). In addition, we examined the effects of CYP when the dose is fractionated to more closely resemble clinical conditions. We hypothesized that multiple, smaller doses of CYP would result in prolonged disruption of salt taste. To evaluate these hypotheses, appetitive qualities of NaCl were tested via brief access methods, and detection thresholds were tested in gustometers for 25 days after the drug treatment regimen. Prior to testing, mice received one of three treatments: 1) five saline injections, 2) five 20mg/kg CYP injections, or 3) four saline injections followed by one 100mg/kg CYP injection. For mice injected with a single dose of CYP, avoidance of NaCl gradually decreased up to day 8 post treatment, then returned to normal by day 10, and briefly decreased again on day 20. The single CYP dose also elevated detection thresholds, peaking on days 6, 14, and 20. The difference in the temporal patterns of disruptions suggests that different systems are being affected by CYP. Five 20mg/kg CYP injections did not alter NaCl preferences, but caused cyclic elevations in NaCl detection thresholds that were more moderate and prolonged disruptions in salt threshold than the single injection. Thus, dosing in a chemotherapy regimen may impact dysgeusia severity and length.

Disclosures: **B.C. Jewkes:** None. **M.G. Gomella:** None. **E.R. Delay:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.23/Y18

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Institutes of Health

National Institute of Allergy and Infectious Diseases

Postgraduate Research Participation Program at the U.S. Army Medical Research Institute of Chemical Defense

Oak Ridge Institute for Science and Education

Title: Organophosphate-induced alterations in plasticity at the hippocampal ca1-schaffer collateral synapse following acute exposure

Authors: *M. EISEN, K. HOFFMAN, E. GLOTFELTY, D. NGUYEN, M. NELSON, P. MCNUTT
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Abstract: Acute poisoning with organophosphorus (OP) cholinesterase inhibitors is a major cause of mortality in the developing world. OP nerve agents (NAs) irreversibly block acetylcholinesterase function, causing accumulation of excess acetylcholine in cholinergic synapses. If untreated, the resulting overstimulation of cholinergic receptors elicits prolonged seizures known as status epilepticus, which can result in neuropsychiatric deficits in survivors. Although central nervous system responses to NA has been studied in chronic animal models, the acute changes in synaptic physiology that are the basis for these pathological circuit dysfunctions have not been well-described. Therefore to better understand the acute synaptic response to OP exposure, we conducted field recordings at the Schaffer collateral-CA1 synapse in hippocampal coronal slices following acute OP application. Specifically, perfusion of soman rapidly elicited a stable reduction of field excitatory post-synaptic potential amplitudes that persisted after wash-out. The concomitant increase in paired-pulse ratios suggests that organophosphate-induced long-term depression (OPi-LTD) results from decreased pre-synaptic release probabilities. To further investigate mechanisms responsible for OPi-LTD, we dissected pre- and post-synaptic signaling pathways characteristically involved in receptor-mediated plasticity. OPi-LTD was blocked by the M1/M3 mAChR antagonists, confirming the role of cholinergic overstimulation in OPi-LTD. For example, OPi-LTD was completely blocked by AM-251, which is an inverse agonist of the cannabinoid type 1 receptor (CB1R). These findings suggest that soman activation of M1 mAChR evokes retrograde endocannabinoid signaling that reduces pre-synaptic release probability via CB1R. Based on these data, we hypothesize that endocannabinoid signaling represents a potential therapeutic modality to mitigate acute and persistent neurological responses to NA exposure. To evaluate the *in vivo* role of CB1R signaling in the central response to soman, the effects of CB1R antagonism on survival were evaluated in a mouse soman exposure model. These studies suggest that manipulation of the central cannabinoid signaling system represents a potential single or adjunctive therapy for OP-induced seizure.

Disclosures: **M. Eisen:** None. **K. Hoffman:** None. **E. Glotfelty:** None. **D. Nguyen:** None. **M. Nelson:** None. **P. McNutt:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.24/Z1

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Defense Threat Reduction Agency – Joint Science and Technology Office, Medical S&T Division

Research Participation Program for the U.S. Army Medical Research and Materiel Command

Oak Ridge Institute for Science Education

U.S. Department of Energy

U.S. Army Medical Research and Materiel Command.

Title: Evaluation of the involvement of forebrain cholinergic projections to the basolateral amygdala in the initiation of nerve agent-induced seizure

Authors: *D. D. PALMER, C. E. KAROLENKO, D. L. SPRIGGS, J. W. SKOVIRA
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Abstract: Seizures induced by organophosphorus nerve agents, such as soman, are believed to be initiated through overstimulation of the cholinergic system. The basolateral amygdala (BLA), a structure known to be highly sensitive to the generating seizure activity, receives cholinergic projections from the medial septum (MS) and substantia innominata (SI). Using an optogenetic approach this study examined whether inhibition by illumination of cholinergic neurons or their projections during seizure onset can modulate the spatial and/or temporal extent of seizure activity. Adult male Long Evans-Tg (ChAT-Cre) rats were surgically prepared 21 days prior to the experiment with cortical screw electrodes to record brain electrocorticograms. An intracranial injection was then made to transduce MS or SI cholinergic neurons using a Cre-inducible recombinant adeno-associated virus vector carrying the Halorhodopsin gene. Optic fiber segments were implanted bilaterally into the MS, SI, or BLA. The indwelling fiber segments were coupled to a DPSS laser (590 nm) during experimentation. Animals received HI-6 (125 mg/kg, IP) 30 min prior to soman exposure (180 µg/kg, SC). Additionally, animals received atropine methyl nitrate (2 mg/kg, IM) at 1 min post-exposure followed by 2-PAM (25 mg/kg, IM) + atropine sulfate (0.5 mg/kg, IM) at 5 min after the onset of seizures to reduce toxic signs and increase survival without affecting seizure activity. Following seizure onset, cholinergic neurons or their projections to the BLA were illuminated, and electrocortical activity was monitored. Our results show that illumination of basal forebrain cholinergic neurons or their

projections to the BLA modulates seizure activity following soman exposure to varying degrees, dependent on the site of optical stimulation.

Disclosures: D.D. Palmer: None. **C.E. Karolenko:** None. **D.L. Spriggs:** None. **J.W. Skovira:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.25/Z2

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH R21AA024641

Title: Histone variants and their turnover in developing rat brain: Effect of Postnatal alcohol exposure

Authors: *N. RACHDAOUI[1], T. KASUMOV[2], D. K. SARKAR[1]
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Abstract: Alcohol exposure during pregnancy leads to a range of disorders known as Fetal Alcohol Spectrum Disorders (FASD). The neurotoxic action of alcohol, i.e. through ROS production, induces DNA damage and neuronal death. Histone variants, particularly H2Ax, H3.3 and H2Az play an important role in the processes of DNA damage repair. HIRA-mediated H3.3 deposition in the DNA damage pathway is crucial to the maintenance of chromatin integrity and restoration of transcriptional activity upon completion of DNA damage repair. We believe that alcohol exposure interferes with these DNA repair processes by affecting the turnover of histone variants. Sprague-Dawley rat pups were fed a milk formula containing 11.34% of ethanol (daily dose of 2.5 g/kg) (alcohol-fed, AF), or an isocaloric liquid diet (pair-fed, PF) from PD2-PD6. Control pups (ad-lib, AD) were allowed to nurse ad-lib. Labeling of histones was done using heavy water (^2H_2O), which was added to the diet during the feeding. First, we measured the effects of postnatal alcohol exposure (PAE) on DNA damage. PAE increased 8-OHdG formation, a marker for DNA double-strand breaks (DSB), in the frontal cortex and hypothalamus of AF rats. PAE significantly increased γH2Ax foci formation, an early marker of DNA DSB, which co-localized with the neuronal marker NeuN. Using ^2H_2O labeling and LC-MS/MS proteomics, we show a differential regulation of histone variants H3.3, H2Az and H2Ax by PAE. H3.3 had a faster turnover rate in the frontal cortex and PAE decreased this turnover rate by ~ 50% with no significant change in the hypothalamus. Turnovers of H2Az and H2Ax were not affected in the frontal cortex but significantly decreased in the hypothalamus. These findings suggest that PAE might impede the DNA repair processes, at least in part, by affecting

histone variants' turnover. The interplay between sustained availability of histone variants and chromatin accessibility of the DNA repair machinery ensure that DNA lesions are faithfully repaired and transcription is resumed.

Disclosures: N. Rachdaoui: None. **T. Kasumov:** None. **D.K. Sarkar:** None.

Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.26/Z3

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NINDS (NS085770)

NIA (AG013854)

Title: Disappearance of tdp-43 inclusions following prolonged transgene expression is associated with cortical atrophy in a conditional transgenic mouse model of ftld

Authors: R. SHAHIDEHPOUR[1], L. KUKREJA[1], G. KIM[1], K. R. SADLEIR[2], H. DONG[4], J. G. CSERNANSKY[3], *M.-M. MESULAM[1], R. J. VASSAR[5], C. GEULA[1]
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Abstract: Dementia due to Frontotemporal lobar degeneration (FTLD) constitutes the third most prevalent dementia after those caused by Alzheimer's Disease and Lewy bodies. A primary pathological marker of FTLD is abnormal precipitation of phosphorylated and mislocalized Tar DNA/RNA-binding protein-43 (TDP-43). Wild-type and mutant TDP overexpression in transgenic animals leads to the formation of inclusions and degeneration. To investigate the temporal sequence of inclusion formation and degeneration in transgenic animals, we employed a conditional transgenic model under the control of the tetracycline operator sequences. Mice were kept on a diet of doxycycline allowing them to mature while keeping the TDP-43 transgene inactive. In line with previous studies, activation of the TDP-43 transgene recapitulated key features of FTLD, including the formation of phospho-TDP-43 neuronal cytoplasmic inclusions. Brains of TDP transgenic mice were cut into 40-µm sections and immunohistochemically processed using an antibody against TDP-43 phosphorylated at Ser-403/404. The number of TDP-43-positive inclusions were quantified in the frontal, temporal and parietal cortex in 10 animals each at the following periods of transgene expression: 5, 10, 14, and 19 days, and 8 and 24 weeks. The area (mm^2) of all investigated cortical regions was measured using Image J as an

indicator of neurodegeneration. Inclusions appeared as early as 5 days after TDP-43 expression, followed by a gradual increase in the number of inclusions until 14 to 19 days of post-weaning expression, when peak inclusion densities were detected. While the 14-day group of mice showed among the highest number of inclusions, cortical measurements revealed no observable atrophy. At 8 and 24 weeks of transgene expression, inclusions were rarely encountered, but the brains showed the most severe degeneration / atrophy. In particular, the piriform cortex contained a high density of inclusions after 14 days of transgene expression with no significant atrophy, while it displayed significant atrophy but only sparse inclusions after 8 and 24 weeks of transgene expression. These observations suggest that, after prolonged transgene expression, TDP-43 inclusions disappear as neurons are lost. They also indicate that the direction of correlation between inclusions and neurodegeneration would be expected to change during the course of disease in FTLD. Our TDP-43 mouse model may be a valuable tool in examining the appearance and disappearance of TDP-43 inclusions and their association with neuronal degeneration.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.27/Z4

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH T32 GM008638

NIH R01 NS082761-01

Title: Neuronal network dysfunction in juvenile neuronal ceroid lipofuscinosis

Authors: R. AHRENS-NICKLAS[1], L. TECEDOR[2], E. BANWELL[3], E. LYSENKO[2], B. L. DAVIDSON[2], *E. MARSH[3]
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Abstract: The majority of metabolic disorders, including two-thirds of lysosomal storage disorders affect the brain. For many of these diseases, including Juvenile Neuronal Ceroid Lipofuscinosis (JNCL, CLN3 disease), it is not understood how the primary biochemical defect leads to central nervous system disease. While many studies of metabolic disease have explored cellular-level pathology, little is known about how these biochemical abnormalities influence

neuronal networks. Ultimately, it is disruption of these networks that leads to neurologic symptoms such as seizures.
We hypothesize that hippocampal hyperexcitability underlies seizures in JNCL. CLN3 protein is expressed throughout the mouse hippocampus early in development, and expression continues in the dentate gyrus into adulthood. Furthermore, both mouse models and human patients demonstrate storage of auto-fluorescent material followed by hippocampal neurodegeneration. GABAergic hippocampal interneurons are especially vulnerable. In this work we investigate the electrophysiology of *CLN3*$^{-/-}$ mice through *in vivo* EEG recordings and voltage sensitive imaging of hippocampal slices from both control and *CLN3*$^{-/-}$ mice.
Compared to age matched control mice, *CLN3*$^{-/-}$ mice have preserved mobility but demonstrate frequent freezing episodes and decreased total movement on analysis of 24hr high-resolution video recordings. On EEG, *CLN3*$^{-/-}$ mice have frequent spikes during periods of normal behavior and high-frequency epileptiform discharges during freezing episodes. Spike quantification revealed that *CLN3*$^{-/-}$ have more spikes at all ages, and that spiking rates were highest in the hippocampus. *CLN3*$^{-/-}$ mice also display differences in background EEG frequency composition, with increased beta and decreased delta activity as compared to controls. This EEG phenotype progresses over the course of the disease.
These results provide the first evidence of a clinically-relevant epilepsy phenotype in a JNCL mouse model. This phenotype can be used in future pathophysiology and drug-development studies of JNCL. Also, studies of human EEG data are needed to evaluate if EEG can be used as a biomarker of disease progression in an individual JNCL patient.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.28/Z5

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: Internal Research and Development

Title: Evaluation of the kinetic properties of cholinesterases from multiple species for nerve agent medical countermeasure model development

Authors: *K. G. MCGARRY, JR, K. E. SCHILL, T. P. WINTERS, J. A. HARVILCHUCK, C. L. SABOURIN, R. A. MOYER
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Abstract: BACKGROUND: Chemical warfare nerve agents (CWNAs) such as sarin and VX continue to be a global threat. Recent events in Syria and the assassination of Kim Jong Nam highlight the ongoing hazards these agents pose to society. Animal models are critical for evaluating the efficacy of CWNA medical countermeasures because it is impractical and unethical to test novel treatments for CWNA poisoning in humans. Therefore, a thorough characterization of available animal models is important for translating results to humans. Disruption of cholinergic function due to inhibition of acetylcholinesterase (AChE) is the primary mechanism of toxicity of CWNAs, and reactivation of inhibited AChE with pralidoxime (2-PAM) is one of the primary therapeutic strategies. CWNAs also inhibit butyrylcholinesterase (BChE) without any apparent toxic effects; rather, BChE acts as a "bioscavenger" that binds CWNAs and removes them from circulation. The degree of inhibition of AChE and BChE, and the effectiveness of 2-PAM are known to vary between species. Thus, the objective of this study was to compare the kinetics of inhibition and reactivation of AChE derived from humans to AChE derived from commonly used large animal models.
METHODS: Red blood cell membranes (RBCs) and plasma were isolated from the whole blood of humans, Yorkshire swine, Göttingen minipigs, and both Indian and Chinese-origin rhesus macaques. The enzymatic activity of AChE and butyrlcholinesterase (BChE) was evaluated in isolated RBCs and plasma that were incubated with VX or sarin and treated with 2-PAM. Enzyme activity was determined using a spectrophotometric assay based on Ellman's method.
RESULTS AND CONCLUSIONS: Both porcine models showed dramatically lower levels of basal BChE activity in plasma compared to macaques and humans. Additionally, AChE from Yorkshire Swine and Göttingen Minipig was more resistant to inhibition by sarin and VX than AChE from the primates. BChE showed a similar trend, although only for sarin. In general, the inhibition and reactivation results fall into two distinct groups (i.e., pig and human/macaque). Taken together, the results indicate that AChE and BChE in the macaques more closely resembles that of humans. Additional research is needed to further elucidate other differences between species (esp. ADME) and which primate model best mimics characteristics of human cholinesterases.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.29/Z6

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS100835

NIH Grant GM103542

Title: Glycation turns mature NGF into a toxic factor for motor neurons

Authors: *M. PEHAR[1], M. KIM[1], B. A. HARLAN[1], K. M. KILLOY[1], J. S. BECKMAN[2], L. BARBEITO[3], M. R. VARGAS[1]
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Abstract: Nerve growth factor (NGF) accumulates in several neurodegenerative diseases associated with increased oxidative and glycating stress. In addition to promote survival, NGF can induce cell death by signaling through the p75 neurotrophin receptor ($p75^{NTR}$). The ability of mature NGF to induce cell death has been extensively reported, but high concentrations, at least an order of magnitude higher than those required to promote cell survival, are required to induce apoptosis *in vitro*. On the other hand, the precursor form of NGF (proNGF) induces cell death at lower concentrations, and the field has focused on the regulation of pro-neurotrophin cleavage as the switch regulating the pro- survival/pro-death signaling of neurotrophins. We have previously shown that nitration of the two tyrosine residues (Tyr52 and Tyr79) present in mature NGF enhances its ability to induce $p75^{NTR}$-dependent motor neuron apoptosis. Here we show that glycation induced by treatment with physiological concentrations of methylglyoxal, mimics the effects induced by tyrosine nitration. Both nitrated- and glycated- NGF formed high-molecular weight-oligomers in solution and induced motor neuron death at physiologically relevant concentrations (sub-picomolar range). In addition, we observed the presence of nitrated- and glycated- NGF in the spinal cord of $hSOD1^{G93A}$ mice, the best characterized mouse model of amyotrophic lateral sclerosis (ALS). Together, our results indicate that the ability of mature NGF to induce cell death can be regulated by post-translational modifications occurring under stress conditions and suggest the potential involvement of post-translational modified-NGF in ALS pathology.

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Poster

136. Mechanisms of Neurodegeneration I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 136.30/Z7

Topic: C.06. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIDA IRP

Title: KDEL receptors - Novel ER stress response genes

Authors: *S. BÄCK[1], K. A. TRYCHTA[2], C. T. RICHIE[2], B. K. HARVEY[2], M. J. HENDERSON[3]
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Abstract: Background: The KDEL receptors serve as a retention mechanism for endoplasmic reticulum (ER) resident proteins that express a KDEL (lysine-aspartate-glutamate-leucine) or KDEL-like C-terminal sequence. These KDEL-containing proteins execute important ER-based functions, such as protein folding and modification, lipid synthesis, and carbohydrate metabolism. By retaining the KDEL-containing proteins in the ER, the KDEL receptors are essential for the maintenance of ER homeostasis.
Objective: Mammals express three KDEL receptor isoform genes - KDELR1, KDELR2, and KDELR3. The biology of the KDEL receptors especially in the central nervous system (CNS) has not been well established. Considering their function in maintaining ER homeostasis, they may play a role in CNS disorders characterized by ER dysregulation and protein misfolding, such as stroke, Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders.
Methods: In order to increase our knowledge about KDEL receptors in the CNS, we performed gene expression analysis using reverse transcription PCR to determine the expression levels of the three KDEL receptors in cell lines, in rat tissue under normal conditions, and in models associated with ER stress.
Results and Conclusions: Our results indicate that the expression of the three KDEL receptors are differently regulated in the cell types and tissues studied both under normal conditions and after induction of ER stress. This would suggest that the KDEL receptors carry out previously unidentified isoform- and tissue-specific functions that may have therapeutic value in diseases characterized by ER stress and accumulation of misfolded proteins.

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Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.01/Z8

Topic: C.07. Ischemia

Support: NIH Health Grant R01 HD049792

Title: Behavioral outcomes following altered serotonin expression and HI-injury in a preterm rat model

Authors: *S. CASAVANT[1], J. M. MCGRATH[2], T. ROSENKRANTZ[3], R. H. FITCH[1]
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Abstract: Children born prematurely (<38 gestational weeks, GW) are at risk for a variety of adverse medical events, and these risks increase with decreasing size/GW. Preterms may experience ischemic and/or hemorrhagic events due to cardiovascular immaturity, leading to hypoxic-ischemic (HI) conditions (low blood and/or oxygen supply) and subsequent neural sequelae. These same infants are exposed to repeated stressful procedures as part of life-saving care within the neonatal intensive care unit (NICU). Although necessary, chronic stressful events have been associated with methylation of the promoter region of the SLC6A4 gene, which codes for serotonin transport proteins. Methylation of this gene due to early adverse conditions has been associated with subsequent reductions in serotonergic tone, as well as anxiety, depression, and increased incidence of autism spectrum disorders. To ascertain the putative influence of chronic stressors on behavioral outcomes associated with a typical preterm HI injury, we assessed male and female rat pups with or without an induced HI injury on postnatal day 6 (P6) -- an age that models a moderately preterm human infant. In addition, pups were treated with a chronic SSRI (Citalopram HBr, 10 mg/Kg) or saline, mimicking the effects of SLC6A4 methylation due to chronic stressors. Subjects were then assessed on a wide range of behavioral tasks, and neuropathologic indices were obtained at the completion of testing. Combined results demonstrate significant interactions between serotonergic anomalies that have been associated with chronic stressors, and an HI injury typical of preterm populations. These findings add to concern regarding adverse effects of stressful experiences in the preterm infant population, particularly in conjunction with existing risks for adverse neurologic sequelae following on early HI events. Results further emphasize the need for additional research on possible mechanisms of neuroprotection for this vulnerable population.

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Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.02/Z9

Topic: C.07. Ischemia

Support: Ontario Brain Institute (OBI)

Kids Brain Health (KBH, formerly NeuroDevNet)

Title: Neural precursor cell (NPC) transplantation in the corpus callosum, as well as constraint-induced movement therapy (CIMT), lead to recovery in the hypoxic-ischemic hemiplegic mouse model

Authors: *P. RUMAJOGEE[1], S. ALTAMENTOVA[1], J. LI[1], L. LI[1], R. S. MENON[2], D. J. VAN DER KOOY[3], M. G. FEHLINGS[4,1]
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Abstract: BACKGROUND:
Cerebral palsy (CP) is the most common pediatric neurodevelopmental physical disability, with a prevalence of 2.3/1000 births, causing severe motor and developmental disturbances. Clinical application of the Constraint-Induced Movement Therapy (CIMT) protocol shows functional benefits in hemiplegic CP. The usage of the child's "less-affected" arm is reduced in order to promote the overuse of the other, affected arm. CIMT has been suggested to trigger neural cell generation from endogenous neural precursor cell (NPC). However, the underlying mechanisms and optimal timing/mode of application remain poorly understood.
METHODS:
To investigate the hemiplegic CP, we use a Hypoxic-Ischemic model (HI) model. The right common carotid artery of post-natal day (PND) 7 C57Bl/6 mice is permanently occluded and, after 2 hours of recovery with the dam, the pups are exposed to hypoxic air (8% oxygen for 45 minutes).
The project has 3 major aspects: 1) Regeneration, which will focus on the effects of NPC transplantation in the corpus callosum (CC), known to be impacted early in the course of demyelinating conditions; 2) Rehabilitation, which will focus on the effects of CIMT; and 3) A third aspect is a combinatorial approach using NPCs and CIMT. NPCs are transplanted in the CC at PND21, while Botulinum toxin (Botox) is injected in 3 muscles of the right (unaffected) forelimb to mimic the CIMT protocol.
RESULTS:
Our results support the use of NPCs and CIMT. We have first validated our HI model as a suitable model to mimic clinical features of CP. The CC morphology is impacted: the oligodendrocyte population is decreased and demyelination is observed. Motor function is also affected: the HI mice use the unaffected forelimb with a clear preference (85% of the time). We have shown that, while only a few co-localizations with neuronal, astrocytic as well as oligodendrocyte markers are seen (<2% each), the NPCs survive and engraft well in the CC. They lead to remyelination and functional recovery: after 1 month, some mice recover completely (50% use of the unaffected forelimb), while others recover only partially (78%). This indirect effect happens likely via the recruitment of endogenous oligodendrocytes in the CC, mediated by the transplanted NPCs. Finally, we have shown a potential synergistic effect between NPCs and CIMT.
CONCLUSION:
This work supports the use of NPC for CP treatment. However, while in our model direct re-

myelination processes still remain to be demonstrated, significant recovery is observed after NPC and Botox treatments. Further investigation is needed in order to decipher the mechanisms of CIMT and a potential synergistic effect with NPCs.

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Poster

137. Perinatal Ischemia

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.03/Z10

Topic: C.07. Ischemia

Support: Dedicated health research funds dedicated from the University of New Mexico

Title: CXCL1/CXCR2 dysregulation as a biomarker of central nervous system injury following *In utero* insult

Authors: T. R. YELLOWHAIR[1], S. NOOR[2], J. R. MAXWELL[3], S. ROBINSON[4], E. D. MILLIGAN[5], *L. L. JANTZIE[6]
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Abstract: Minimizing central nervous system (CNS) injury from preterm birth depends on identification of critical pathways underlying essential neurodevelopmental programs and CNS pathophysiology. While chorioamnionitis (CHORIO) is a known precursor to brain injury in preterm infants, the precise mechanisms linking prenatal injury and long-term CNS damage are unknown. We hypothesized that the chemokine CXC-ligand 1 (CXCL1) and its receptor CXCR2, would be dysregulated in CNS injury concomitant with a persistent immune response, including neutrophil trafficking, in our preclinical model of CNS injury associated with preterm birth. Using an established model of CHORIO in rats that results in deficits in the mature CNS that mimic those of children born preterm, uterine arteries were occluded for 60 min, and lipopolysaccharide (LPS) was injected into amniotic sacs on embryonic day 18 (E18). Pups were born at term (E22). SB225002, a CXCR2 antagonist, was administered intraperitoneally from postnatal day 1 (P1)-P5 (3 mg/kg). Brain, serum and placenta were collected from E19 to P15 and analyzed using multiplex electrochemiluminescence, Western blot, qPCR and flow cytometry (FC) with n=4-8/group (t-test or ANOVA with Bonferroni correction with $p<0.05$ indicating statistical significance). Compared to shams, CHORIO increased placental CXCL1

(153±23 vs 94±15 pg/100μg, $p<0.01$) and yielded sustained serum CXCL1 elevation through P15 ($p<0.05$). Notably, brain CXCL1 remained elevated in CHORIO rats compared to sham from P2 ($P<0.05$) through P7 ($p<0.001$). FC in brain lysate showed increased $CXCR2^{+}$ neutrophils and microglia in CHORIO compared to shams (all $p<0.05$). CXCR2 antagonist, SB225002, reduced cerebral neutrophil activation, gliosis, and αII-spectrin cleavage at P7, indicative of improved neural cell health ($p<0.05$). These data show a sustained systemic and neuroinflammatory response following CHORIO in rats. Further characterization of neuroinflammatory signaling pathways will facilitate identification of brain and serum injury biomarkers and advance new therapeutic strategies. Cellular and molecular biomarkers of prenatal injury and neuroinflammation may be clinically useful to stratify newborns with CNS injury for treatment with emerging interventions.

Disclosures: T.R. Yellowhair: None. **S. Noor:** None. **J.R. Maxwell:** None. **S. Robinson:** None. **E.D. Milligan:** None. **L.L. Jantzie:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.04/Z11

Topic: C.07. Ischemia

Support: NIH K08NS101122

Title: Neuronal activity during acute seizures associated with hypoxic-ischemic injury in neonatal mice

Authors: *J. BURNSED[1], M. DARLING[2], P. WAGLEY[3], J. KAPUR[4]
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Abstract: Background:Neonatal seizures are common and the majority are due to hypoxic-ischemic encephalopathy (HIE). Use of tissue clearing, transgenic mice, and advanced microscopy allow neuronal activity mapping in many disease states. Circuitry involved in acute HIE-associated seizures is unknown and may shed light on the relation between early seizures and later behavioral deficits. **Objective**:Examine neuronal activity and evolution following acute HIE seizures in a neonatal mouse model using tissue clearing and microscopy.
Methods:Postnatal day (p)9 mice are implanted with electrodes for electroencephalography (EEG). On p10 HIE is created using modified Vannucci method (unilateral carotid ligation + 45 min of 8% hypoxia) in Cre-tamoxifen transgenic mice (TRAP). Injection of 4-hydroxytamoxifen 1 hr following hypoxia allows expression of fluorescent protein in active neurons during the 1-2hrs prior. EEG is performed during this time. Sham mice receive incision + anesthesia without

hypoxia or ligation. p17 mice are perfused and tissue is processed using lipid-clearing protocol. Multiphoton imaging and Zeiss Zen software is utilized to obtain and process images (tiling and creation of z-stacks of thick slices of tissue), Imaris 8.2 is used for analysis. **Results**:Tissue clearing and multiphoton microscopy allowed visualization of active neurons in the TRAP mouse during acute HIE-associated seizures. Preliminary results show HI mice exhibit selective neuronal activation in the dentate granule cell layer and CA3 areas hippocampus compared to sham. Both groups exhibit activity in the somatosensory cortex. **Conclusion**:Tissue clarification and advanced microscopy provide a feasible method for examining neuronal circuit activity during seizures in this model. Neuronal activity is present in the bilateral dentate gyrus and CA3 of HI mice (injected 1 hour after hypoxia). Ongoing work uses these methods to delineate seizure evolution and correlate EEG findings with neuronal activity in this model.

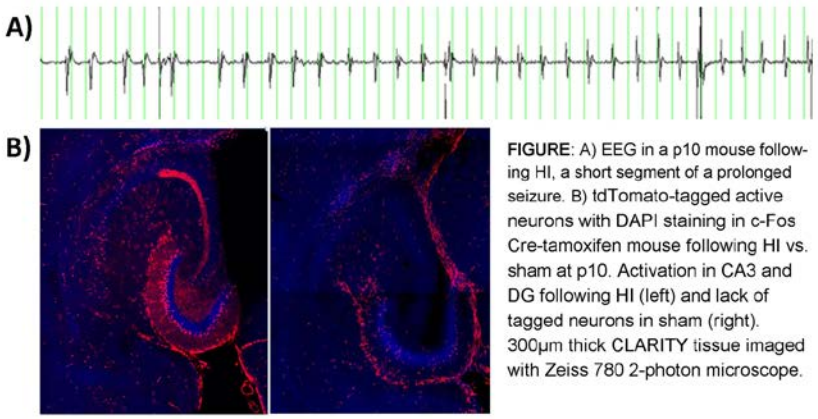

FIGURE: A) EEG in a p10 mouse following HI, a short segment of a prolonged seizure. B) tdTomato-tagged active neurons with DAPI staining in c-Fos Cre-tamoxifen mouse following HI vs. sham at p10. Activation in CA3 and DG following HI (left) and lack of tagged neurons in sham (right). 300μm thick CLARITY tissue imaged with Zeiss 780 2-photon microscope.

Disclosures: **J. Burnsed:** None. **M. Darling:** None. **P. Wagley:** None. **J. Kapur:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.05/Z12

Topic: C.07. Ischemia

Title: Maternal immune activation sensitizes the neuroinflammatory responses to neonatal hypoxia-ischemia in offspring brains

Authors: *H.-R. CHEN, N. MANDHANI, Y.-Y. SUN, C.-Y. KUAN
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Abstract: Epidemiological evidence suggests that intrauterine infection is a risk factor for autism spectrum disorders (ASD), as supported by ASD-like cognitive deficits in animal models of maternal immune activation (MIA). However, since not all human MIA offspring develop ASD, “second hits” may be instrumental to cause severe brain damage and disruption of the neural network. In the present study, we tested this hypothesis using a well-established MIA model with Poly I:C (20 mg/kg), a synthetic analogue of double-stranded RNA that activates Toll-like receptor 3, intraperitoneally injected at mid pregnancy (E12.5) in C57BL/6 mice. The offspring were collected and challenged by the Rice-Vannucci model of HI (unilateral common carotid artery ligation followed by 60-min exposure to 10% oxygen at 37^0 C) at P10 as the second hit. We found that MIA alone infrequently caused clusters of amoeboid microglial cells (AMCs) expressing a high level of Complement component 3 (C3) in the offspring brains. Elevated NFκB signaling and a higher basal level of IL-6, IL-17 and MMP9 mRNA were also detected in the P11 MIA offspring brains. When challenged by HI, the MIA offspring showed significantly greater NFκB activity (more nuclear p55/ NFκB and less cytoplasmic IκB), TUNEL-positive apoptosis, and mRNAs for a multitude of pro-inflammatory cytokines, including IL-6, IL-17, TNFα, IL-23, TSPO and MCP-1 at 24 h post-injury, when compared to those injured by HI alone. At 7 d recovery, the MIA/HI-injured mice showed more AMCs, monocyte infiltration, and greater brain atrophy than singularly MIA- or HI-injured mice. Finally, the MIA/HI-injured mouse brains showed a significant reduction of PSD95 and synaptotagmin/PSD-95 punctates, correlated with greater C3 expression in the hippocampal CA2/3 region than MIA alone or HI-injured counterparts. In conclusion, these results suggest that MIA elevates the inflammatory activity in the offspring brain, and acts as a primer to sensitize the neuroinflammatory responses to a secondary HI insult, leading to greater brain damage. The two-hit model may explain why only a subset of MIA offspring develop ASD-like cognitive impairments. Future studies are needed to unravel the mechanisms of MIA-induced neonatal immune dysregulation.

Disclosures: **H. Chen:** None. **N. Mandhani:** None. **Y. Sun:** None. **C. Kuan:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.06/Z13

Topic: C.07. Ischemia

Support: Department of Physical Therapy and Human Movement Sciences, Northwestern University

Title: Quantification of the flexion synergy and reach kinematics in pediatric hemiplegia

Authors: *N. M. HILL[1,2], J. P. A. DEWALD[1,2,3]
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Abstract: *Introduction:* Pediatric hemiplegia results from injury to the developing brain before, during or soon after birth. After such injury, an individual can present with involuntary joint coupling between shoulder abduction (SABD) and elbow flexion (EF), known clinically as the flexion synergy. The expression of the flexion synergy during reaching has been shown to increase with SABD loading in adults post stroke but has not yet been characterized in PH. Retention of high resolution ipsilateral corticospinal projections in earlier injuries may reduce the presence of involuntary joint coupling that is characteristic of adults post stroke. The aim of this study is to quantify reach distance during a dynamic task as a function of SABD loading in PH. It is hypothesized that individuals with earlier injuries (PRE) will be able to reach farther at higher SABD loads compared to those with later injuries (PERI and POST). *Methods:* Participants included 5 individuals with PH (ages 10y-19y; 3 PRE, 1 PERI, 1 POST). Maximum voluntary SABD torque was determined isometrically for each participant. Participants then completed a set of reaching tasks in the Arm Coordination Training 3-D (ACT^{3D}) robot. The ACT^{3D} is admittance-controlled and allows arm movement in three dimensions. With the arm rigidly coupled to the robot, participants were instructed to reach forward towards a virtual target set near full arm extension. Each set of reaches required participants to lift their arm against different loads including full support on a haptic table and 20%, 35%, 50%, 65% and 80% of SABD max. To compare results between participants, reach distance was normalized to a percentage of maximum distance achieved on the table. *Results:* Percent change from the table condition to each SABD level was calculated for the paretic arm where a negative value indicates a decrease in distance. The mean change at 20% was -4%±13% (PRE), -8% (PERI), and 2.5% (POST) and at 80% was -12%±7% (PRE), -23% (PERI), and -51% (POST). These preliminary results show a decrease in reach distance at higher SABD levels with a trend towards greater deficits in individuals with later injuries. *Conclusions:* Use of retained ipsilateral corticospinal projections may enable the relative maintenance of reach ability seen across load levels in earlier injured individuals. In contrast, a reliance on more diffuse reticulospinal projections may explain the decreased reach ability seen in later injuries. Knowledge gained from further study will enable deeper understanding of neural pathways as well as the development of targeted therapies to address the underlying causes of motor impairments in subpopulations of PH.

Disclosures: N.M. Hill: None. **J.P.A. Dewald:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.07/Z14

Topic: C.07. Ischemia

Support: Pediatric Discovery Funds from the Department of Pediatrics, University of Mississippi Medical Center

Newborn Medicine Funds from the Department of Pediatrics, University of Mississippi Medical Center

NIH Grant NIH/NINDS RO1NS080844

Title: Intrauterine growth restriction is associated with long-lasting brain impairments and behavioral dysfunction

Authors: N. B. OJEDA[1], J. W. LEE[1], S. LU[1], E. C. TURBEVILLE[1], C. B. MUNCIE[2], L.-T. TIEN[3], *Y. PANG[4], L.-W. FAN[1]
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Abstract: Epidemiological and experimental studies suggest that intrauterine growth restriction (IUGR) can cause neurodevelopmental impairments. Our previous studies demonstrated that IUGR alters brain size and behavioral performances in both neonatal and juvenile rats. To further examine the long-lasting effects of IUGR, a rat model of IUGR induced by reduction in uterine perfusion during late gestation (E14 to E22) was used in the current study of 6 month old rats. Nissl staining and immunohistochemistry techniques (MAP2: dendrites; RIP: myelin; Iba1: microglia and GFAP: astrocytes), and behavioral tests (locomotor activity) were performed to examine brain impairments and behavioral dysfunction. Our results indicated that reduced uterine perfusion resulted in IUGR offspring with significantly lower birth weight compared to control offspring. At 6 months, IUGR offspring showed significant decreases in locomotor activity, as indicated by the reduction of total traveled distance. IUGR offspring also showed significant reduction of total brain, cortical, and hippocampal volume, and increased ventricle volume. Moreover, IUGR offspring showed significant brain impairments as indicated by dendrite (MAP2+) and myelin (RIP+) deficits, as well as increased brain inflammation, as indicated by the increased numbers of microglia and astrocytes. These results suggest that IUGR causes long-lasting behavioral disturbances and persistent brain changes, which may be associated with increased brain inflammation. This model may be useful for studying mechanisms involved in the development of brain changes associated with IUGR and for developing future potential therapeutic strategies.

Disclosures: **N.B. Ojeda:** None. **J.W. Lee:** None. **S. Lu:** None. **E.C. Turbeville:** None. **C.B. Muncie:** None. **L. Tien:** None. **Y. Pang:** None. **L. Fan:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.08/Z15

Topic: C.07. Ischemia

Support: the National Natural Science Foundation of China (No. 31660289)

Innovation Fund of Nanchang University for Graduate Students (No.cx2016318)

Title: Oxytocin exerts neuroprotective effects on neonatal rat hippocampal CA1 pyramidal neurons after hypoxic-ischemic injury by enhancing the inhibitory synaptic transmission

Authors: *C. XIE[1], J. WU[2], T. LIU[2], S. PENG[2], J. WU[2], L. XIAO[2]
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Abstract: Objective: Neonatal hypoxic ischemic encephalopathy (NHIE) is one of the most prevalent causes of death or lifelong disability in children. Thus, it is urgent to seek for new and more effective neuroprotective therapy to minimize the consequences of HIE. Previous studies have shown that oxytocin can improve learning and memory ability after ischemic stroke of adult rats. Here, we ask whether oxytocin has neuroprotective effects on neonatal rats with hypoxic-ischemic injury.
Methods: Brain slices of 350 μm thickness from 7-10 days old Sprague-Dawely rats were used. Visualized whole-cell patch-clamp recordings were obtained from hippocampal CA1 pyramidal neurons. An in-vitro model of hypoxic-ischemic cell injury was used by exposing the brain slices to oxygen-glucose deprivation (OGD) solution for 10 min or longer.
Results: In 12 out of 16 neonatal CA1 pyramidal neurons, bath application of oxytocin (0.1 μM) induced an inward current (16.11 ± 1.98 pA) at a holding potential of -70 mV under voltage-clamp recording, which suggest a probable effect of exogenous oxytocin on CA1 pyramidal neurons. Therefore, when switched to current-clamp (I=0), we observed that oxytocin significantly prolonged the onset time of anoxic depolarization from 13.44 ± 1.84 min to 23.19 ± 2.04 min after the superfusion of OGD solution. Interestingly, both oxytocin receptor antagonist dVOT and GABA
receptor antagonist bicuculline occluded this effect. Moreover, oxytocin increased both the amplitude and frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) in a concentration-dependent manner but had no significant influence on spontaneous excitatory postsynaptic currents (sEPSCs) in CA1 pyramidal neurons. In addition, the facilitation effect of oxycin on IPSCs was blocked by either tetrodotoxin or dVOT.
Conclusion: Oxytocin exerts a neuroprotective effect by enhancing the inhibitory synaptic

transmission through oxytocin receptors in neonatal CA1 pyramidal neurons. Therefore, oxytocin could be used as a candidate for neuroprotective treatment after NHIE.

Disclosures: C. Xie: None. **J. Wu:** None. **T. Liu:** None. **S. Peng:** None. **J. Wu:** None. **L. Xiao:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.09/Z16

Topic: C.07. Ischemia

Title: Loss of neurons at retina ganglion cell layer in rats under prenatal hypoxia-ischemia

Authors: *L. S. FONSECA[1], G. M. DINIZ-TAVEIRA[1], F. TENORIO[1], P. C. BARRADAS[1], T. E. KRAHE[2]
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Abstract: Prenatal hypoxia-ischemia is one of the main causes of neurodevelopmental impairment in the newborn and is associated with cerebral palsy, attention problems, hyperactivity, epilepsy, and sensory alterations, including visual processing problems. Although the deleterious effects of hypoxia-ischemia on brain development are known, many of the mechanisms involved in this process remain to be elucidated. Considering that the retina is widely recognized as a neural circuit model used in the study of the development and plasticity of neuronal circuits, the investigation of the effects of prenatal hypoxia-ischemia on retinal development offers great potential to elucidate mechanisms related to the effects of hypoxia-ischemia during pregnancy. Based on this premise, this study aimed to evaluate the effects of prenatal systemic hypoxia-ischemia on the retinal cytoarchitecture of Wistar rats. Here we used an experimental model of prenatal hypoxia-ischemia in which the flow of the uterine arteries of pregnant Wistar rats was interrupted for 45 minutes on the eighteenth gestational day (HI group, n = 4 rats). Control animals were obtained from pregnant females submitted to the same surgical procedures except for the occlusion of the uterine arteries (SH group, n = 4 rats). Histological and immunohistochemical processing of the retinas was done in the second, ninth, twenty-third, and thirtieth postnatal days. Sagittal retinal sections of the HI group stained with hematoxylin and eosin (HE) revealed that although the cytoarchitecture of the retinas was preserved, quantification of the number of cells in the ganglionic layer of the retinas stained with HE revealed no differences between the experimental groups at all ages analyzed. Interestingly, quantification of the number of neurons in the retinal ganglion layer immunohistochemically labeled for NeuN showed a significant reduction in the number of neurons in animals that suffered prenatal hypoxia-ischemia. The absence of differences in the number of cells in the

retinal ganglion layer of the retinas stained by HE and the reduction in the number of NeuN-labeled neurons suggests that there was an increase in the number of other cell types in this layer following prenatal hypoxia-ischemia. Based on our results we can conclude that prenatal hypoxia-ischemia causes profound and long-lasting changes in the morphology of the retina of rats.

Disclosures: L.S. Fonseca: None. **G.M. Diniz-Taveira:** None. **F. Tenorio:** None. **P.C. Barradas:** None. **T.E. Krahe:** None.

Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.10/Z17

Topic: C.07. Ischemia

Support: UNICO foundation

Title: Astrocyte activation in the hypoxic newborn piglet brain

Authors: *S. N. MALAEB[1], A. R. GARCIA[3], M. DELIVORIA-PAPADOPOULOS[1], R. RAGHUPATHI[2]
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Abstract: Cerebral hypoxia and ischemia (HI) results in astrocyte activation, which can persist long after HI. It is known that astrocytes respond to insults by forming numerous gap junctions (GJ) near degenerating neurons. When cells are compromised, messages are transmitted to neighboring cells by GJs and cause otherwise unaffected cells to also die. Interventions for neuroprotection are most effective when given to slow the progression of injury before permanent damage is established. The time course at which astrocyte activation following hypoxia is most pronounced in the newborn brain remains unclear. The present study tests the hypothesis that hypoxia results in long-term astrocyte activation in the newborn piglet brain. Ventilated newborn piglets were exposed to hypoxia [Hx; FiO_2 0.07 for 1hr, titrated for PaO_2 goal of 20-25 mmHg and hypotension (40% decrease in systolic BP)], then returned to FiO_2 0.21. Normoxic piglets remained in FiO_2 0.21. The animals were euthanized at 1 day, 3 days, 7 days post hypoxia. The brains were perfusion fixed and stored in 4% formaldehyde. Tissue sections from comparable regions of the hippocampus were stained for evidence of astrocyte activation, such as upregulation of GFAP expression, as well as for neuronal damage. Hypoxia resulted in severe cellular damage at 1 day, 3 days, 7 days post hypoxia, manifested as changes of apoptosis and necrosis with pyknotic nuclei, ruptured or irregular bordered nuclear membranes and non-prominent nucleoli. Astrocyte activation was more pronounced at 7 days

compared to 3 days post Hx. Reactive astrocytes were observed in the white matter tracts in the sulci and along blood vessels in the gray matter. We conclude that hypoxia resulted in neuropathology and astrocyte activation that persisted for several days following hypoxia in newborn piglets. Hypoxia induced brain injury is multifactorial in nature and involves oxidative stress, mitochondrial dysfunction, excitotoxicity, intercellular signaling, inflammation, programmed cell death and necrotic cell death. Damaged neurons are replaced by astroglial scar tissue. Targeting factors that regulate astrocyte activation after hypoxia can lead to novel strategies for neuroprotection.

Disclosures: S.N. Malaeb: None. **A.R. Garcia:** None. **M. Delivoria-Papadopoulos:** None. **R. Raghupathi:** None.

Poster

137. Perinatal Ischemia

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Topic: C.07. Ischemia

Support: NIH Grant U54HD079123

NIH Grant R01HD076901

Cerebral Palsy Foundation

Title: Effects of dendrimer-conjugated N-acetyl-L-cysteine in combination with hypothermia in a mouse model of neonatal hypoxic-ischemic encephalopathy

Authors: M. S. GARCIA[1], R. REDDY[2], P. CARR[1], S. DOMAN[1], L. GOMPERTZ[1], A. FATEMI[1], M. V. JOHNSTON[1], R. M. KANNAN[2], S. KANNAN[3], *M. WILSON[1]
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Abstract: Perinatal hypoxic-ischemic encephalopathy (HIE) is a risk factor for cerebral palsy (CP) and other neurodevelopmental disorders. Although therapeutic hypothermia has significantly improved neurobehavioral outcomes for infants after perinatal HIE, there is a critical need for complementary therapies that will improve and sustain its neuroprotective effects. A novel therapy using hydroxyl-terminated polyamidoamine (PAMAM) dendrimer nanoparticles to deliver N-acetyl cysteine (NAC) has shown very strong neuroprotective effects in a rabbit LPS-mediated maternal inflammation model of CP and in a preterm white matter injury model after ischemia at P5. We have shown previously in a mouse model of perinatal HIE that these dendrimer nanoparticles can deliver N-acetyl-L-cysteine (NAC) to activated microglia,

astrocytes and injured neurons when administered 0 to 24h after HI. Dendrimer-conjugated NAC (D-NAC) uptake increases with injury, with greatest uptake in microglia treated at 24h, and hypothermia does not impair uptake of D-NAC.
In this study, we used a mouse model of perinatal HIE to investigate the effects of combining hypothermia with D-NAC, administered within 24h of HI. CD1 mice were subjected to hypoxic-ischemia (HI) on post-natal day 7 (P7), induced by right common carotid ligation and exposure to 10% O_2 (15 min, 36.5 °C), followed by 6 hours of either hypothermia (33.6 ^{o}C) or normothermia (37 ^{o}C). D-NAC (10 mg/kg, i.p.) or vehicle was administered 0, 6 or 24 h after HI. Brain injury was examined using a volumetric analysis of ipsilateral and contralateral hemispheres in Nissl-stained sections 7 days later. As expected, brain injury was reduced in vehicle-treated mice subjected to hypothermia, with a significant correlation between brain injury and body temperature at 6h (Pearson's $R2=0.23$, $p<0.01$). We found an unexpected interaction between D-NAC and hypothermia, in which treatment with D-NAC at 6h or 24h interfered with the neuroprotective effects of hypothermia. We hypothesize that this is related to hypothermia-induced changes in the microglial response, and current studies are focused on understanding the microglial responses to hypothermia over time. Results support our hypothesis that microglial responses to HI are important in determining outcome after neonatal HI, and that when administered at the optimal interval after HI, D-NAC will improve neuroprotection. By studying the effects of combined hypothermic treatment and targeted nanotherapy with D-NAC, we hope to contribute to clinical advances in the treatment of perinatal HIE.

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Poster

137. Perinatal Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 137.12/Z19

Topic: E.06. Posture and Gait

Support: NIH 5R01NS081936-03

Title: Regional modulation of tetrahydrobiopterin determines predilection for hypertonia following antenatal hypoxia-ischemia

Authors: *M. BAJAJ[1], S. TAN[1], G. NATARAJAN[1], A. SHARMA[1], M. MAHASETH[1], K. LUO[1], Z. SHI[1], A. DROBYSHEVSKY[2], J. VASQUEZ-VIVAR[3], K. THIRUGNANAM[3]
[1]Wayne State Univ., Detroit, MI; [2]Pediatrics, Northshore Univ. Hlth. Syst. Res. Inst., Evanston, IL; [3]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Background: Tetrahydrobiopterin (BH4) is thought to be critical for neuronal survival after hypoxic-ischemic (HI) injury. We have previously shown that MRI biomarkers can predict which fetuses will develop postnatal hypertonia following antenatal hypoxia-ischemia (HI) Objective: We hypothesized that perturbations in BH4 biosynthetic pathway in regions of the brain predispose to hypertonic injury after HI. Further, we explored gender differences in BH4 concentrations in various brain regions. Methods: In vivo global HI of fetuses was induced in pregnant New Zealand white rabbits at 25 days gestation with a 4F Fogarty balloon catheter in a 3T magnet. Using MRI determinations of brain apparent diffusion coefficient (ADC), we categorized fetuses predicted to get hypertonia or not, based on criteria of ADC decrease below a nadir of 80% and presence of evidence of reperfusion-reoxygenation injury (n=58 and 20 respectively). BH4 concentrations were assayed using HPLC-electrochemical detection. The gene expression of BH4 biosynthetic enzymes, GTPCH, PTPS, SPR, and recycling enzyme, DHPR, DHFR, were correlated with BH4 concentrations. GTPCH, the first biosynthetic enzyme, and histone deacetylase (HDAC) assays were also assayed by automatic Western Blot (Wes, Protein Simple). Statistical analyses used ANOVA and t-test. Results: There were significant between-group differences in BH4 concentrations immediately after HI in the cerebellum (ANOVA p=0.002) and thalamus (ANOVA p=0.039), but not in the cerebral cortex or basal ganglia. Gene expression of DHFR was the only enzyme that corresponded to low or high BH4 levels. There were no gender differences in BH4 concentrations in the various brain regions in any group. To explore whether there were any epigenetic associations, we compared HDAC concentrations in cerebral cortex between groups and found no differences. Conclusions: The lower BH4 concentrations in the thalamus and cerebellum immediately after HI insult in the groups predicted to have hypertonia, compared to those without injury suggests that BH4 may be a novel pathophysiologic pathway for motor injury following HI. It is speculated that an intrinsic deficiency of brain BH4 may predispose to critical injury leading to hypertonia.

Disclosures: M. Bajaj: None. **S. Tan:** None. **G. Natarajan:** None. **A. Sharma:** None. **M. Mahaseth:** None. **K. Luo:** None. **Z. Shi:** None. **A. Drobyshevsky:** None. **J. Vasquez-Vivar:** None. **K. Thirugnanam:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 138.01/Z20

Topic: C.07. Ischemia

Support: Grant-in-Aid for JSPS Fellows 16J04127

Title: BDNF mRNA delivery using biocompatible nanomicellar carrier treats delayed neuronal death via enhanced neuroprotective effects of astrocytes

Authors: *Y. FUKUSHIMA[1], K. ITAKA[2], H. IMAI[1], S. UCHIDA[3], K. KATAOKA[3], N. SAITO[1]
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Abstract: Despite decades of trials to develop neuroprotective treatment against ischemic neuronal death, there is no internationally prevalent effective agents. These difficulties are particularly due to problems of drugs for central nervous systems: neurotoxicity and barriers to efficient delivery. Here, we conceived of a therapeutic strategy of brain-derived neurotrophic factor (BDNF)-expressing mRNA delivery against ischemic neuronal death using our biocompatible nanomicellar carrier, which facilitates rapid and stably-continuous expression of the encoding proteins for days. Theoretically, this mRNA induction strategy which enables brain cells, including neurons and glial cells, to secrete BDNF in situ, has a possibility of overcoming those problems. A rat model of transient global ischemia, which causes delayed neuronal death in hippocampal CA1 neurons, was treated by intraventricular injection of BDNF mRNA. Immuno-histochemical analyses revealed that intraventricular injection of BDNF mRNA increased BDNF expression particularly in astrocytes. The BDNF expression lasted about 3 days in hippocampus by ELISA.
A single injection of the mRNA on 2 days after ischemia (DAI) provided a remarkable effect of preventing cell death on 6 DAI. Interestingly, the effect was greater than those when the mRNA was injected on 1 and 3DAI, suggesting that the optimal timing of injection would not be immediate post-ischemic period, but a few days after the ischemic attack. For pursuing the prolonged neuroprotective effect, we set the schedule of injecting twice on 2 and 5DAI. Eventually, the effect of preventing cell death of CA1 neurons was confirmed even in the chronic phase of ischemic attack (13 and 20DAI). These results suggest that BDNF mRNA is a promising agent for treating ischemic neuronal death by enhancing neuroprotective effect of astrocytes. Especially, the lag period of a few days after the ischemic attack to obtain maximal

therapeutic effect by the mRNA injection offers the advantage in clinical usage for acute ischemic diseases of the brain.

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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 138.02/Z21

Topic: C.07. Ischemia

Support: Training Grant 2T32EY013933

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DoD Grant DURIP

Title: Vascular endothelial caspase-9 activity drives edema, neuronal death, and vision loss following retinal vein occlusion

Authors: *M. I. AVRUTSKY[1,1], Y. Y. JEAN[1], A. J. WHITE[1], S. SNIPAS[2], G. S. SALVESEN[2], C. M. TROY[1]
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Abstract: INTRODUCTION: The retina is the most metabolically active tissue in the body, rendering it sensitive to vascular dysfunction. Consequently, diseases that disrupt normal retinal blood supply, including retinal vein occlusions (RVO) and diabetic retinopathy, are the leading causes of blindness in working-age adults. Despite available therapies, an estimated 50% of patients do not respond to treatment.
METHODS: We employed a mouse model of retinal vein occlusion (RVO), achieved by tail-vein injection of rose bengal, followed by laser photocoagulation of retinal veins. *In vivo* analyses - optical coherence tomography (OCT) and electroretinograms (ERGs) - were conducted with the Micron IV system (Phoenix Research Labs). RVO induces acute retinal edema, which peaks during the first 24 hours following injury. Over a 7 day time course the edema resolves, revealing a permanent retinal thinning due to death of retinal neurons.
RESULTS: We identified caspase-9, a protease traditionally associated with apoptosis, as an essential mediator of edema. Increased levels of activated caspase-9 were detected in vascular endothelial cells 1 hour following RVO. We tested RVO in mice with inducible endothelial-cell-

specific deletion of caspase-9 (C9 ECKO). Compared to littermate controls, C9 ECKO mice developed less edema, and sustained less retinal degeneration after RVO injury. ERG analysis of retinal function showed that C9 ECKO mice preserved better response to light stimulus. To study whether inhibiting caspase-9 would provide protection against RVO we utilized a novel caspase-9 inhibitor, which we can deliver to the retina using simple eyedrops. Treatment of wildtype mice with the caspase-9 inhibitor immediately after induction of RVO provides morphologic, biochemical and functional retinal protection. Inhibition of caspase-9 reduces edema, protects retinal morphology, and helps prevent vision loss following RVO injury. Our studies indicate that endothelial caspase-9 plays an essential role in regulating edema pathogenesis. Moreover, our novel cell permeant caspase-9 inhibitor abrogates the edema and may be a potential therapy for individuals suffering from vascular eye disease.

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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

Support: CNPq

CAPES

UEM

University of Maastricht

Title: Roflumilast, a phosphodiesterase 4 inhibitor, promotes memory recovery and attenuates white matter injury of aged rats with chronic cerebral hypoperfusion

Authors: *R. M. OLIVEIRA[1], A. N. SANTIAGO[2], L. M. SOARES[2], J. PRICKAERTS[3], H. MILANI[2]
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Abstract: Chronic cerebral hypoperfusion (CCH) is a prodromal feature of aging-related dementia, including Alzheimer's disease type. Hippocampal neurodegeneration and white matter injury contribute to the cognitive impairments frequently observed in CCH conditions. The permanent stepwise occlusion of the vertebral arteries (VAs) and internal carotid arteries (ICAs),

the 4-VO/ICA model, is a model of CCH which promotes persistent memory loss and neurodegeneration in aged rats. The phosphodiesterase type 4 inhibitor roflumilast presents pro-cognitive properties in several behavioral paradigms. Here, we evaluated the effects of chronic roflumilast treatment in aged rats (18-20 months old) subjected to 4-VO/ICA model of CCH. Fifteen days before the surgery, aged rats were trained in a non-food-rewarded eight-arm aversive radial maze (AvRM) in order to learn the task. Roflumilast (0.003 mg/kg and 0.01 mg/kg) was *i.p.* administered during 29 days, once a day. Retrograde memory performance was assessed at 7, 14, 21, days of CCH in the AvRM. We also investigated the effects of roflumilast on hippocampal neurodegeneration and white matter injury by Nissl and Kluver-Barrera staining, respectively. CCH caused a persistent memory deficit in aged rats, as indicated by increased latency and number of errors in the AvRM. Additionally CCH aged rats showed hippocampal neurodegeneration and vacuolization and fiber disarrangement in the white matter. Repeated roflumilast treatment restored the cognitive impairments induced by CCH in aged rats, yet in the absence of neuronal rescue. Attenuation of white matter injury was also detected in the *optic tract* of CCH aged rats treated with roflumilast. The present data suggest that roflumilast might be used as a potential pharmacological strategy for the treatment of cognitive sequelae associated with CCH.

Disclosures: R.M. Oliveira: None. **A.N. Santiago:** None. **L.M. Soares:** None. **J. Prickaerts:** None. **H. Milani:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Shanghai Youth Eastern Scholar Program (QD2015037)

Shanghai Pujiang Scholar Program (15PJ1407700)

Title: Buyang Huanwu decoction prevents infiltration of natural killer cells and improves ischemic outcomes in a rat model of transient focal cerebral ischemia

Authors: *Z. WANG, B. DOU, W. ZHOU, S. LI, L. WANG, S. ZHU
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Abstract: Brain ischemia activates a cascade of the immune responses which are initiated by the infiltration of immune cells. Natural killer (NK) cells are innate lymphocytes and among the first immune cells that respond to an ischemic insult in human brains. The infiltration of NK cells

results in neuronal death and exacerbates brain infarction. Buyang Huanwu Decoction (BYHWD), a classic formula of traditional Chinese medicine, has long been used for treatment of ischemic stroke. The present study was to investigate whether BYHWD would prevent infiltration of NK cells and improve ischemic outcomes in a rat model of transient focal cerebral ischemia. Male Sprague-Dawley rats were subjected to middle cerebral artery occlusion (MCAO) for 60 minutes followed by reperfusion for 3 days. BYHWD was orally administrated at the onset of reperfusion followed by another injection 12 hours later, then twice daily. Treatment with BYHWD markedly reduced brain infarction, increased the retention time on an accelerating rotarod, and attenuated blood-brain barrier (BBB) breakdown on day 3 after reperfusion. Matrix metalloproteinases (MMPs), especially gelatinases (MMP-2 and 9), are known to be up-regulated in cerebral ischemia and contributes to BBB disruption. In our study, both MMP-2 and 9 activities were robustly increased in the ischemic cortex of MCAO rats on day 3 after reperfusion, and BYHWD significantly reduced the increased activities, as assessed by gelatin zymography. As a result, the degradation of tight junction proteins was inhibited by BYHWD. Infiltration of NK cells was observed in the ischemic cortex using flow cytometry, and this infiltration was remarkably blunted by treatment with BYHWD. The mRNA level of chemokine CXCL10 was significantly increased after ischemia/reperfusion and was markedly inhibited by BYHWD. As observed using confocal microscopy, CXCL10 was mainly produced by endothelial cells in the ischemic cortex. Altogether, our results demonstrate that BYHWD may prevent ischemic endothelial cells from recruiting NK cells, and therefore preserve BBB integrity and improve ischemic outcomes.

Disclosures: Z. Wang: None. **B. Dou:** None. **W. Zhou:** None. **S. Li:** None. **L. Wang:** None. **S. Zhu:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

Support: Department of Anatomy PhD Scholarship

Title: Delayed post-treatment with adult-sourced adipose-derived MSCs is neurorestorative of striatal DARPP-32 neurons after neonatal rat HI

Authors: *B. E. AGHOGHOVWIA, D. E. OORSCHOT
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Abstract: Perinatal hypoxia-ischemia (HI) is a major cause of striatal injury and may lead to cerebral palsy. Delayed post-treatment with bone marrow-derived mesenchymal stem cells

(MSCs), at one week after neonatal rat HI, was neurorestorative of striatal medium-spiny projection neurons. An even better clinical option may be adult-sourced adipose-derived MSCs because of their easily accessible subcutaneous location and a growth factor secretome that is ~90% similar to bone marrow-derived MSCs. Hence, the aim of this study was to investigate whether delayed post-treatment with adult-sourced adipose-derived MSCs, at 7 to 9 days after neonatal rat HI, was neurorestorative of striatal medium-spiny projection neurons following HI-induced brain injury. On postnatal day (PN) 7, male Sprague-Dawley rat pups were weight-matched, exposed to either HI right-sided brain injury or no HI injury, and assigned to groups (n = 4/group) - untreated (HI+Dil), normal controls (Normal+Dil), single stem cell-treated (HI+MSCs×1) and double stem cell-treated (HI+MSCs×2). On PN14 and 16, all groups were treated with either diluent or stem cells. All animals were then perfused on PN21. Serial 5µm thick frozen sections were cut coronally through the brain using a cryostat and immunohistochemically stained for striatal dopamine- and cAMP-regulated phosphoprotein-(DARPP)-32-positive spiny projection neurons. The absolute number of these neurons was estimated using the Cavalieri's and Abercrombie/unfolding methods. There was a significant difference in the absolute number of DARPP-32-positive neurons in the striatum when the four groups were compared (one-way ANOVA, Friedman non-parametric test, $p < 0.033$, Prism). Post-hoc comparisons revealed a significant increase in the absolute number of striatal DARPP-32 neurons in the HI+MSCs×2 group and normal control group compared to the HI+Dil group ($p < 0.042$, two-tailed; $p < 0.043$, one-tailed, respectively; adjusted for multiple comparisons). There was an increase in the absolute number of striatal DARPP-32 neurons in the HI+MSCs×1 group, but this was not statistically significant. These results suggest that delayed double treatment with adult-sourced adipose-derived MSCs has therapeutic potential for rescuing striatal neurons after neonatal HI.

Disclosures: B.E. Aghoghovwia: None. **D.E. Oorschot:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

Support: CONACYT 241655

Title: Quantification of S-allylcysteine (SAC) in different regions of rat brain. Hippocampus as the main site of SAC accumulation

Authors: *R. AVALOS-CHACON, S. ROJAS, P. MALDONADO
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Abstract: Garlic (*Allium sativium)* has been used for different purposes in many cultures; many preparations of garlic have been developed; one of them is the aged garlic extract (AGE). SAC is an organosulfur aminoacid generated during garlic aging which is the main component present in AGE. A large number of studies have demonstrated the antioxidant activity of SAC; some of the antioxidant mechanisms reported are the following ones: 1) scavenges reactive oxygen (ROS) and nitrogen (RNS) species; 2) increases enzymatic and nonenzymatic antioxidant levels, and 3) inhibits some prooxidant enzymes. Nowadays SAC has been studied as a potent drug for neurodegenerative diseases, which incidence has increased in the recent years. SAC has been proved to have antioxidant and neuroprotective effect against oxidative stress damage, which can be generated in diseases such as ischemia. It is known SAC's pharmacokinetics and that it has a high bioavailability when oral administrated. However, it has not been studied the amount of SAC present in different brain regions after oral administration. We developed a bioanalytical method to quantify SAC in cortex, stratium and hippocampal brain rat using HPLC-UV detector method. The developed bioanalytical method was validated according to the Bioanalytical Method Validation Guide emitted by the FDA. After this, samples from stratium, cortex and hippocampus from healthy and ischemic animals were quantified. Healthy animals were administered with SAC (1g/Kg, i.g.) and 30 min later the tissues were extracted and prepared for chromatographic injection. For the next group of animals, a surgery was performed to occlude the medial cranial artery for 1 hour and then a reperfusion for 24 hours, after that, they were administrated with SAC (1g/Kg, i.g.) and 30 min later the tissues were extracted and prepared for chromatographic injection. It is observed that in normal conditions hippocampus is the brain region where mainly SAC is accumulated. The cortex is the brain region in which less amount of SAC was quantified. Under ischemia/reperfusion conditions, where exists a flow blood alteration, it is observed a significant increase in the amount of SAC quantified in the right side of the stratium and hippocampus compared with normal conditions. Probably due to the blood brain barrier (BBB) disruption occurred during the ischemia/reperfusion event. However, hippocampus was again the brain region where a greater amount of SAC was quantified. According with these findings, it is possible to propose SAC as a therapeutically agent for diseases where the hippocampus is affected, such is the case of Alzheimer disease.

Disclosures: R. Avalos-Chacon: None. **S. Rojas:** None. **P. Maldonado:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Academia Sinica in Taiwan

Title: Therapeutic potential of Clinacanthus nutans against ischemia-reperfusion injury through the PPAR-γ signaling pathway

Authors: *J.-S. WU, M.-H. KAO, H.-D. TSAI, W.-M. CHEUNG, T.-N. LIN
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Abstract: BackGround and Objective: Clinacanthus nutans (CN) a popular traditional medicine in Southern Asia for infection, inflammation, cancer, and Diabetes treatment. But, there has no report on ischemic stroke therapy yet. Ligand-activated PPAR-γ is known for its anti-inflammatory, anti-diabetes, and neuroprotective effects. In this study, we aimed to investigate whether CN protects against ischemic brain injury via PPAR-γ signaling. **METHODS:** To investigate the protective effects of CN against stroke. Primary cortical neurons were subjected to oxygen/glucose deprivation-reoxygenation (H-R) *in vitro* hypoxic model. MTT assay was used to detect cell viability. Flowcytometry was used to monitor mitochondrial membrane potential (MMP), apoptosis. Reporter assay was used to detect the transcriptional activity of PPAR-γ. RT/PCR and Western blot were used to detect PPAR-γ mRNA and protein expression. For *in vivo* study, rats were subjected to 3-vessel occlusion (MCAO)/reperfusion. Neurological deficit scores and infarct volumes were used to evaluate functional and cellular damage. **RESULTS:** *In vitro:* CN significantly increased cell viability, maintained MMP, and reduced apoptosis compared to vehicle control at hypoxia 30mins and 1 day reperfusion (H.5R24). Results of western blot indicated CN inhibited OGD induced caspase-3 activation and PARP cleavage. However, the protective effect was abrogated by GW9662 (a PPAR-γ antagonist), suggesting the protective effect of CN was through PPAR-γ pathway. Results of RT-PCR analysis further conformed CN increased PPAR-γ expression significantly at H.5R24. Moreover, reporter assay found that CN increased PPAR-γ promoter activity, indicating CN increased PPAR-γ level in a transcriptional regulation. *In vivo*: CN significantly reduced infarct brain volumes in rat subjected to 30-min ischemia and 1-day reperfusion. But, the protective effect was abrogated by GW9662. Furthermore, CN improved motor functional recovery even after 2-weeks reperfusion. **CONCLUSIONS:** We report that CN confers therapeutic potential for ischemic brain damage. CN via upregulating PPAR-γ transcription to inhibit mitochondria dependent apoptosis in ischemic brain.

Disclosures: J. wu: None. **M. Kao:** None. **H. Tsai:** None. **W. Cheung:** None. **T. Lin:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Support: NIH R01HL128546

Title: Impact of mesenchymal stem/stromal cell administration on microglial activation during cardiopulmonary bypass surgery

Authors: K. SARKISLALI[1], F. A. SOMAA[1], G. R. STINETT[1], P. D. MORTON[1], B. LEWIS[4], M. M. NUSZKOWSKI[2], E. K. MONTAGUE[2], L. ROESCH[3], P. J. HANLEY[3], J. A. FRANK[4], R. A. JONAS[1], *N. ISHIBASHI[5]
[1]Children's Natl. Heart Inst. and Ctr. for Neurosci. Res., [2]Cardiac Surgery, [3]Program for Cell Enhancement and Technologies for Immunotherapy, Div. of Blood and Marrow Trans, Children's Natl. Hlth. Syst., Washington, DC; [4]Frank Lab. and Lab. of Diagnos. Radiology Research, Dept. of Radiology and Imagi, NIH, Bethesda, MD; [5]Childrens Natl. Med. Ctr., Washington, DC

Abstract: Survivors of congenital heart disease (CHD) frequently have poor neurodevelopmental outcomes after surgery. Cardiopulmonary bypass (CPB) surgery can trigger prolonged microglial activation in white matter (WM). Rodent studies have shown that mesenchymal stem/stromal cells (MSCs) regulate microglia activation. Clinical trials have established the safety of MSC-based therapy. CPB allows intra-arterial administration of MSCs through the ascending aorta in children with CHD. In order to design optimal MSC-based therapies for the CHD population, we aimed to determine the: i) distribution of MSCs after delivery through CPB; ii) effects of MSCs on clinically-relevant physiological biomarkers; and iii) effects of MSCs on CPB-induced microglia activation. Two-week old piglets were randomly assigned to one of 3 groups: (1) Control (no surgery), (2) Severe CPB insult (circulatory arrest for 60min) or (3) Severe CPB insult followed by MSC administration. In group 3, superparamagnetic iron oxide (SPIO)-labeled MSCs (10×10^6 per kg) were delivered through the aortic cannula during the rewarming period after circulatory arrest. Animals were sacrificed 3hrs after CPB. SPIO distribution was evaluated with MRI and immunohistochemistry. Iba1 and CD11b were used to define microglial activation. We found a diffuse distribution of hypointense voxels (SPIO particles) throughout the entire brain by T2* weighted MRI. Large clusters of hypointense voxels were also detected along both lateral and third ventricles. Histological analyses revealed an even distribution of SPIOs within the cortex and WM. We have previously demonstrated disruption of the blood-brain barrier and an increase in permeability after circulatory arrest. Consistently our analyses identified SPIOs located in the extra-vascular space, suggesting that CPB is an efficient administration system for MSC delivery. Various biomarkers after MSC delivery did not differ compared with CPB group. Additionally, no evidence of either embolic events or microstrokes were observed by MRI and histology. These results suggest no negative impact of MSCs in the acute period after surgery. CPB resulted in an increase in microglial numbers compared with Control. MSC administration reduced this response throughout the cortex and WM. Together, our results demonstrate that MSC delivery during CPB is highly effective and shows translational potential to minimize CPB-induced microglial activation in children with CHD.

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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

Title: A role of microglia in the progression of ischemic brain edema

Authors: *M. TANAKA[1], Y. ISHIHARA[1,2], K. ITOH[3], A. ISHIDA[1], T. YAMAZAKI[1]
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Abstract: Brain edema is the fatal complications of the ischemic stroke. The leading cause of brain edema is considered as the extravasation of fluid into the cerebral parenchyma induced by disruption of the blood-brain barrier. Recently, increasing evidence shows that microglia are activated in the ischemic region and that proinflammatory cytokines enhance vascular permeability. Therefore, we investigated a role of microglia on brain edema progression. Male mice were subjected to permanent middle cerebral artery occlusion (pMCAO). They were studied at 3, 6, 12, 24 h after occlusion with magnetic resonance imaging (MRI) and 2,3,5-triphenyl tetrazolium chloride (TTC) staining to visualize edema and infarct, respectively. Brain water contents and neurological scores were measured 24 h after pMCAO. Microglial activity was assessed by immunohistochemistry of Iba1 and CD68 at the same time points with MRI. Minocycline, a tetracycline derivative with microglia blocking effects was intraperitoneally administrated 1 h before surgery. Hyperintensities in DWI and T2WI were detected in ischemic hemisphere 3 and 6 h, respectively, after pMCAO. Brain water contents in ischemic hemisphere increased compared with those in the contralateral hemisphere. These results showed that cytotoxic edema was induced a couple of hours after ischemia, followed by the formation of vasogenic edema. When we visualized infarct area by TTC staining 12 and 24 h after pMCAO and merged the staining image with T2WI, it is revealed that vasogenic edema was transferred from ischemic area to non-ischemic area over time. Microglia in the region of vasogenic edema showed not only the enlargement of soma but also increased CD68 expression, indicating that microglia are strongly activated. Interestingly, microglial morphologic change and increases in phagocytic activity were also observed the peripheral area of vasogenic edema region. Treatment with minocycline clearly inhibited microglia activation accompanied with ischemia. Minocycline suppressed increases in brain water contents as well as impairment of neurological score 24 h after ischemia, suggesting that activated microglia under ischemia could be involved in edema

progression. Microglia activation initially observed in the ischemic region can be introduced into the peripheral regions, which could elicit, at least in part, the enlargement of vasogenic edema. We would define this transmission of microglial activity “microglial wave”, and suppression of microglial wave is considered to be significant to minimalize neuronal injury caused by ischemic brain edema.

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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Support: NIH Grant R01HL071568

Title: Dendrimer-based N-acetyl-L-cysteine therapy improves long term outcomes after cardiac arrest in a rat model

Authors: *H. R. MODI[1], Q. WANG[2], S. J. BERTRAND[4], S. KANNAN[3], R. KANNAN, 21210[2], N. V. THAKOR[1]
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Abstract: Cardiac arrest (CA) entails significant risks of coma resulting in poor neurological and behavioral outcomes after resuscitation. Significant subsequent morbidity and mortality in post-CA patients are due largely to the cerebral dysfunction that accompanies prolonged whole-body ischemia called as Post-CA syndrome (PCAS). PCAS involves strong inflammatory responses including neuroinflammation. Currently, there are no proven neuroprotective therapies to improve post-CA outcomes apart from therapeutic hypothermia. Furthermore, there are no acceptable approaches which can target neuroinflammation and lead to good neurological outcome post-CA. Moreover, delivering drugs across the blood-brain barrier to the target injured cells for treating diffuse brain injury is a major challenge. We hypothesize that dendrimer-based N-acetyl-L-cysteine (D-NAC) therapy ameliorates neuroinflammation and leads to a marked improvement in post-CA neurological outcome. We used an asphyxic CA rat model to determine the effects of D-NAC treatment. D-NAC was administer 30-minute post return of spontaneous circulation after cardiopulmonary resuscitation (ROSC). The behavioral neurologic deficit score (NDS score) was evaluated at 4, 24 and 48 hrs post-CA. Overall there was a dramatic decrease in NDS score following CA. D-NAC treatment increased NDS scores compared to the saline group.

We also tested long term (7 days) behavior outcome (novel object and fear conditioning) post-CA. Seven days post-CA performance on novel object and fear conditioning tasks was evaluated. Administration of D-NAC decreases freezing behavior in a novel context suggesting a long-term cognitive effect of D-NAC. In sum, acute administration of D-NAC following CA results in physiological and behavioral improvements.

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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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University of Leon

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Title: Anti-oxidant response in cerebral cortex and hippocampus in an oxygen and glucose deprivation (OGD) *Ex vivo* model. The effect of BDNF

Authors: *P. GONZALEZ-RODRIGUEZ[1], I. F. UGIDOS[1], D. PEREZ-RODRIGUEZ[1], B. ANUNCIBAY-SOTO[1], E. FONT BELMONTE[1], C. PEREZ-GARCIA[2], J. M. GONZALO-ORDEN[2]
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Abstract: Brain derived neurotrophic factor (BDNF) has been suggested as a possible palliative or even regenerative therapy against stroke, one of the first cause of death in worldwide. Here we report how the oxidative stress is modified in an oxygen and glucose deprivation (OGD) model followed by the return to normoxic condition (reperfusion-like, RL), as well as the effect of the presence of BDNF on this stress. The study was carried out on 350 µm thick slices of hippocampus (Hp) and cerebral cortex (Cx) above it and were analyzed at different times of RL with and without the presence of 50 ng/ml BDNF. Lipid peroxidation was measured as a marker of oxidative stress. OGD/RL significantly increased these levels and the presence of BDNF in the RL decreased the OGD/RL-induced lipid peroxidation. One of the mechanisms to overcome the cell oxidative stress rise is mediated by the Nuclear factor erythroid 2-related factor 2 (Nrf2),

responsible for the regulation of a large number of enzymes with an anti-oxidant role, including nqo1 (NADPH quinone dehydrogenase 1), hmox1 (heme oxygenase 1), gpx (glutathione peroxidase 1), gclm (glutamate cysteine ligase, modifier subunit) or sod2 (superoxide dismutase 2), among others. We measured the transcriptional expression and the activity of both, Nrf2 and anti-oxidant enzymes, in Cx and Hp slices. Interestingly, OGD/RL resulted in a progressive reduction of the anti-oxidant activity and transcriptional expression in Cx slices. In contrast, a late significant Sod and total anti-oxidant activity increase was observed in the Hp slices. The presence of BDNF attenuated or led to normoxic levels the markers analysed in both Hp and Cx slices. Therefore, we concluded that Hp and Cx present differences in the cell oxidative stress response induced by OGD/RL. Besides, the presence of BDNF reduces the cell oxidative stress induced by OGD modifying the levels of anti-oxidant activity and transcriptional expression.
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Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Title: AT1 receptor antagonism related modulation of stroke induced motor dysfunction and neuronal damage

Authors: *V. GUPTA, A. KUMAR
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Abstract: Objective: To investigate the neuroprotective potential of Angiotensin II Type 1 (AT1) receptor blocker Azilsartan against global cerebral ischemia induced brain injury in Wistar rats.
Methods: Bilateral common carotid artery occlusion (30min Ischemia and 48hr reperfusion) was performed in wistar rats for the induction of global cerebral ischemia. Pre treatment with Azilsartan (2 and 4mg/Kg; *p.o.*) starting 7 days prior to BCCAO till the end of reperfusion was done.

Results: Pre treatment with azilsartan restored the behavioral function (as assessed by locomotor activity, rota rod performance, hanging latency and neurological score), arrested oxidative stress (as assessed by LPO, GSH, SOD, catalase and nitrite), decreased infarct area (as seen by TTC staining) and recovered histological alterations (as seen by H&E staining).
Conclusion: Pre treatment with azilsartan protects the brain from neuronal damage after global cerebral ischemia in wistar rats.

Disclosures: V. Gupta: None. **A. Kumar:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

Support: NIH SBIR Grant 4R44NS095420-02

Title: Translational studies on treatment of stroke with a selective ROCK2 inhibitor, BA-1049

Authors: *M. D. ABBINANTI, J. RUSCHEL, F. YANG, K. M. ROSEN, L. J. MCKERRACHER
BioAxone BioSciences, Cambridge, MA

Abstract: Dysregulation of Rho Kinase (ROCK) is involved in multiple vascular pathologies, including stroke. ROCK2, an isoform of ROCK, regulates cell-cell junctions in endothelial cells, a critical component of the blood-brain barrier (BBB). In animal models, ROCK inhibitors reduce infarct size and improve functional recovery after stroke. Despite endothelial cells being a potential target cell type to improve recovery after stroke, there are no effective therapies that target increased BBB permeability after ischemia, a defect further aggravated during reperfusion injury. We are developing intravenous (IV) and oral formulations for a ROCK2-selective inhibitor, BA-1049, as drug candidates to treat the neurovascular disorders stroke (IV administration) and cavernous malformation (oral administration). Safety pharmacology, pharmacokinetic, and pharmacodynamic studies indicate that BA-1049 has appropriate drug-like properties for further development. To investigate the ability of BA-1049 to reverse ROCK activation in brain endothelial cells, we used the transient middle cerebral artery occlusion (tMCAO) model in mice and followed two biomarkers of ROCK activation, phosphorylated cofilin and phosphorylated myosin light chain 2 (MLC2). We performed a randomized, masked study with male and female mice, occluding the MCA for sixty minutes followed by administration of BA-1049 within thirty minutes of the onset of reperfusion. Administration of BA-1049 reduced levels of phosphorylated cofilin and phosphorylated MLC2 on the stroke side of the brain as compared to vehicle-treated controls. In dose-response studies, this reduction was

detectable at intraperitoneal (IP) doses as low as 1 mg/kg. In time-course studies, the reversal of ROCK activation was sustained at least 24 hours after a single dose. Iba1 antibody staining showed BA-1049 administration reduced activated microglia on the stroke side of the brain. To investigate efficacy of BA-1049 to restore BBB function, Evans blue dye was administered after tMCAO. We found that BA-1049 can restore the BBB after stroke compared to vehicle-treated controls. Repeat-dose, oral administration studies in mice demonstrate a promising safety profile and therapeutic window. These preliminary data show that BA-1049 may be an effective treatment to address pathological vascular dysfunction and permeability in the brain after stroke.

Disclosures: M.D. Abbinanti: A. Employment/Salary (full or part-time):; BioAxone BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAxone BioSciences. **J. Ruschel:** A. Employment/Salary (full or part-time):; BioAxone BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAxone BioSciences. **F. Yang:** A. Employment/Salary (full or part-time):; BioAxone BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAxone BioSciences. **K.M. Rosen:** A. Employment/Salary (full or part-time):; BioAxone BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAxone BioSciences. **L.J. McKerracher:** A. Employment/Salary (full or part-time):; BioAxone BioSciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BioAxone BioSciences.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 138.14/AA1

Topic: C.07. Ischemia

Support: NS095420

Title: The novel ROCK2-selective inhibitor BA-1049 restores barrier function of human brain endothelial cells depleted of cerebral cavernous malformation (CCM) proteins

Authors: *K. M. ROSEN[1], J. RUSCHEL[1], T. S. SHISHOIAN[2], M. D. ABBINANTI[1], M. S. MORITZ[2], R. STOCKTON[2], L. J. MCKERRACHER[1]
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Abstract: Cerebral cavernous malformation (CCM) is a cerebrovascular disorder characterized by cystic endothelial brain lesions with defective vascular barrier function, which are susceptible to hemorrhage and causing hemorrhagic stroke. CCM is caused by CCM1, CCM2 or CCM3 loss-of-function mutations in brain endothelial cells with loss of barrier function. Studies of familial CCM reveal that the disease-characteristic disruption of the neuroendothelial barrier is caused by overactive Rho kinase (ROCK) leading to endothelial cell contraction, opening of cell-cell junctions and extravasation of blood constituents into the brain. To date no disease-modifying pharmacological treatment for CCM is approved. We have developed a novel ROCK inhibitor, BA-1049, to normalize ROCK overactivation after CNS trauma. BA-1049 possesses an 80-fold higher selectivity for ROCK2, which is the ROCK isoform predominantly expressed in the neurovascular endothelium as we revealed by proteomic analysis. Therefore, we determined the potential of BA-1049 as a pharmacological treatment for CCM using disease-relevant cell culture assays. In human umbilical vein endothelial cells (HUVECs), simulated with lysophosphatidic acid (LPA) to induce endothelial ROCK overactivation, BA-1049 reduced actin-myosin contraction, as shown by reduced phosphorylation of myosin light chain 2 (MLC2) and actin stress fibers. Moreover, BA-1049 preserved adherens junction organization and prevented disintegration of the HUVEC monolayer. To examine the efficacy of BA-1049 when brain endothelial cells display CCM loss-of-function, we silenced CCM1, CCM2 or CCM3 gene expression in human brain microvascular endothelial cells using RNAi. Similar to LPA-stimulated HUVECs, depletion of CCM proteins led to increased phospho-MLC2, stress fiber formation and actin-myosin contraction resulting in increased monolayer permeability, all of which could be prevented by treatment with BA-1049. Finally, we determined whether BA-1049 possesses features of an orally available compound. Pharmacokinetic analysis of rodents orally dosed with BA-1049 showed good bioavailability and the presence of an active metabolite, termed BA-2017. Metabolic profiling revealed that rodent, monkey and human, but not canine hepatocytes produce the primary metabolite BA-2017. Strikingly, the metabolite BA-2017 showed a higher affinity to ROCK2 as well as greater potency for ROCK2 inhibition in comparison to its parent BA-1049. Taken together these data suggest that BA-1049 is a promising, orally available therapeutic for clinical development toward a first treatment for human CCM patients.

Disclosures: K.M. Rosen: A. Employment/Salary (full or part-time):; Bioaxone Biosciences Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bioaxone Biosciences Inc. **J. Ruschel:** A. Employment/Salary (full or part-time):; Bioaxone Biosciences Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bioaxone Biosciences Inc. **T.S. Shishoian:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bioaxone Biosciences Inc. **M.D. Abbinanti:** A. Employment/Salary (full or part-time):; Bioaxone Biosciences Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bioaxone Biosciences Inc. **M.S. Moritz:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bioaxone Biosciences Inc. **R. Stockton:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Bioaxone Biosciences Inc. **L.J. McKerracher:** A. Employment/Salary

(full or part-time):; Bioaxone Biosciences Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Bioaxone Biosciences Inc..

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 138.15/AA2

Topic: C.07. Ischemia

Support: Colciencias 11565740581

Scholarship Colciencias 647

Title: Anti-inflammatory effect by regulation of lipid species in brain and serum: Linalool neuroprotection in a cerebral ischemia model

Authors: *A. M. SABOGAL, N. C. CORTES, J. A. GUTIERREZ, R. A. POSADA, G. P. CARDONA
Univ. of Antioquia, Medellin, Colombia

Abstract: Cerebral ischemia is caused by the blockage of blood vessels in the brain. Different types of treatments have been evaluated to block or delay the progression of this disease without success yet. In this study, the effect of Linalool was evaluated in an *in vitro* model using a glutamate excitotoxicity model (125 μM), and *in vivo* with a global ischemia model in Wistar rats. Linalool was given orally: 25 mg / kg every 24 hours for 1 month, during this time, behavioral tests were developed. In addition, lipidomic analysis was performed by mass spectrometry and gas chromatography. Our *in vitro* results show protection by Linalool (100 nm) in neurons and astrocytes greater than 50%, reduction of lipid peroxidation and recovery of ATP levels. *In vivo,* animals treated with Linalool had a faster neurological recovery than control animals, accompanied by better motor and cognitive performance. These results were confirmed by the significant reduction of astrogliosis, microgliosis and markers of inflammation in the hippocampus; involving the recovery of the PI3K / PTEN ratio, free fatty acids 24:0 , and the recovery of the profile of phospholipids composed of mono and polyunsaturated fatty acids (PC 36: 1; 42: 1 (24: 0/18: 1) / LPE 22: 6 / LPC22: 6) in the hippocampus. In addition, the serum regulation of PI 36: 2 and other LCFA (long chain fatty acids). In summary, oral administration of linalool produces an anti-inflammatory effect post-ischemia through the regulation of lipid species in parenchyma and serum.

Disclosures: A.M. Sabogal: None. **N.C. Cortes:** None. **J.A. Gutierrez:** None. **R.A. Posada:** None. **G.P. Cardona:** None.

Poster

138. Therapeutic, Interventional, and Translational Studies in Ischemia

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Topic: C.07. Ischemia

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NIH Grant NRCDP (K Kahle)

Simons Foundation SFARI Grant (K Kahle)

Title: Neuroprotective effects of SPAK inhibition in ischemic stroke and malignant cerebral edema

Authors: *M. I. BHUIYAN[1], H. HUANG[1,2], M. N. HASSAN[1], V. M. PIGOTT[1], B. J. MOLYNEAUX[1,3], T. ZHANG[4], X. DENG[4], J. ZHANG[5], K. T. KAHLE[6], D. SUN[1,7]
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Abstract: The WNK-SPAK/OSR1 kinase complex controls renal salt reabsorption and systemic blood pressure by regulating ion transporters and channels. Its activation in the central nervous system after ischemic stroke is associated with brain swelling, grey matter injury, and demyelination. We recently reported that genetic deletion of the WNK3-SPAK kinase complex in mice improves radiographic and clinical outcomes in malignant cerebral edema after ischemic stroke. In this study, we investigated the efficacy of pharmacological inhibition of WNK-SPAK kinase complex with three novel pharmacological inhibitors in a mouse model of focal ischemic stroke (middle cerebral artery occlusion, MCAO) in male adult C57BL/6j mice. At 3 hours reperfusion, mice were randomly assigned to receive vehicle DMSO (2 ml/kg body weight, i.p.), the pan-WNK-kinase inhibitor WNK463 (2.5 mg/kg, i.p.), recently demonstrated SPAK inhibitor closantel (CLS, 0.1-10 mg/kg, i.p.) or a novel SPAK inhibitor and CLS analog ZT-1a (2.5-5 mg/kg, i.p.). Infarct volume, hemisphere swelling, neurological deficits, and expression of phosphorylated SPAK and NKCC1 proteins in ischemic brains were analyzed. The vehicle control group exhibited 76.3 ± 28.3 mm^3 infarct volume and 20.5 ± 4.5 % hemisphere swelling at

24 hours post-MCAO. WNK kinase inhibitor WNK463 did not significantly reduce infarct volume (77.1 ± 27.5 mm^3) or hemisphere swelling (20.0 ± 5.6 %). In contrast, SPAK inhibitor CLS exhibited a dose-dependent (0.1-10 mg/kg) neuroprotection with no apparent adverse effects. Interestingly, the novel SPAK inhibitor ZT-1a (5 mg/kg) significantly reduced infarct volume by 35 % and hemisphere swelling by 50%. We will investigate ischemia-mediated up-regulation and phosphorylation in SPAK-NKCC1 in the CLS- and ZT-1a-treated brains. These results strongly suggest that SPAK kinase activity is associated with ischemic brain damage and pharmacological inhibition of SPAK-NKCC1 complex has therapeutic potentials for stroke therapy.

Disclosures: **M.I. Bhuiyan:** None. **H. Huang:** None. **M.N. Hassan:** None. **V.M. Pigott:** None. **B.J. Molyneaux:** None. **T. Zhang:** None. **X. Deng:** None. **J. Zhang:** None. **K.T. Kahle:** None. **D. Sun:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Program#/Poster#: 139.01/AA4

Topic: C.09. Brain Injury and Trauma

Support: Center for Neuroscience and Regenerative Medicine 306136-16.01-60855

NIAAA Intramural Research Program

The Uehara Memorial Foundation

Title: Fear extinction learning and glial function changes after mild traumatic brain injury (mTBI) from blast

Authors: *M. NONAKA[1], O. BUKALO[1], W. TAYLOR[1], A. POSTLE[1], L. B. TUCKER[2], A. H. FU[2], Y. KIM[2], J. T. MCCABE[2], A. HOLMES[1]
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Abstract: Mild TBI is the most common form of acquired brain injury, and in military and civilian settings it can result from exposure to a blast. In some cases, mild TBI from blast exposure results in long term cognitive and emotional symptoms, including depression or post-traumatic stress disorder (PTSD). Following single or repeated blast exposure in male mice, trends in fear extinction learning and retrieval/renewal were observed at various time points after the injury. Independent RT-qPCR analysis for glial markers using the same animals revealed altered expression of myelin-related genes in the hippocampus 2-4 weeks after blast and a more widespread effect 8 weeks after blast. Myelin basic protein staining by immunohistochemistry

supported these alterations at the protein level. Further study is underway to determine the effects of blast-induced mild TBI on myelin regulation.

Disclosures: **M. Nonaka:** None. **O. Bukalo:** None. **W. Taylor:** None. **A. Postle:** None. **L.B. Tucker:** None. **A.H. Fu:** None. **Y. Kim:** None. **J.T. McCabe:** None. **A. Holmes:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: NICHD grant HD061963

Merit Review grant from Veteran's Administration

Title: The dopamine D1 receptor antagonist, SCH 23390, reverses cognitive deficits following mild traumatic brain injury in the adolescent female rat

Authors: *L. L. KRAFJACK[1], J. W. HUH[2], R. RAGHUPATHI[1]
[1]Drexel Univ. Col. of Med., Philadelphia, PA; [2]Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Following mild traumatic brain injury (TBI), girls perform more poorly on visual memory tasks and take longer to recover from their symptoms than their male counterparts. The cellular mechanisms of these sex differences are unknown. To model mild TBI in adolescents, anesthetized 35 day-old rats were directly impacted on the skull using a 5mm metal tip just behind bregma over the midline suture (2mm depth, 5.5m/s velocity); sham-injured rats were anesthetized, but not injured. We have previously reported that female, but not male, adolescent rats subjected to this mild TBI exhibit a deficit in novel object recognition (NOR) memory at 3 days post-injury. The dopaminergic system has been implicated in post-traumatic cognitive dysfunction and alterations in receptor activity and expression may underlie spatial and working memory deficits following moderate-severe TBI. We hypothesized that hyper-activation of the D1 subtype of the dopamine receptor may mediate injury-induced NOR memory impairments. Sham- and brain-injured female rats were administered varying doses of the D1 receptor antagonist SCH 23390 immediately after injury. Sham-injured rats displayed impaired NOR memory following administration of the high dose of SCH 23390 (0.02mg/Kg), but were unaffected by the low dose (0.01mg/Kg). Neither dose of SCH 23390 (0.01 or 0.02 mg/Kg) administered at the time of injury was effective at preventing the injury-induced NOR memory deficits. We also assessed whether administration of SCH 23390 at the time of behavioral testing would affect NOR memory deficits. At both doses of SCH 23390 (0.02 or 0.05mg/Kg), sham-

injured rats were impaired in NOR memory. However, the low dose of SCH 23390 (0.02mg/Kg) completely reversed the injury-induced deficits, whereas the high dose (0.05mg/Kg) was not effective. These observations suggest that delayed alterations in the dopamine system may underlie these acute cognitive deficits in brain-injured female rats.

Disclosures: L.L. Krafjack: None. **J.W. Huh:** None. **R. Raghupathi:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: U.S. Army Research Office grant W911NF-14-2-0087

NIH grant 5R25GM077634-04

Title: Detonations of military explosives aimed at hippocampal slice cultures lead to distinct changes in synaptophysin, GluR1, and NCAM-180 staining in dendritic fields

Authors: M. F. ALMEIDA[1], T. PIEHLER[2], M. C. PAIT[1], R. BENJAMIN[2], H. W. ROMINE[1], *B. A. BAHR[1]
[1]Biotech. Res. and Training Ctr., Biotech Ctr. / William C. Friday Lab., Pembroke, NC; [2]US Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: Different levels of traumatic brain injury occur due to explosive shockwaves, and they represent the most common injury associated with military service. To study the neuronal effects after survivable blasts, an experimental protocol was developed that generates distinct blast waves from cyclotrimethylene trinitramine (RDX) military explosives directed at cultured cells and brain slices (Zander et al. 2015 J Neurosci Res 93:1353; Smith et al. 2016 Exp Neurol 286:107; Zander et al. 2017 Cell Mol Neurobiol; Piehler el al. 2017 Military Med). Here, direct effects of RDX detonations on brain tissue were assessed, using rat hippocampal slice cultures. The cultured tissue slices were sealed in serum-free media and the containment lowered into a water-filled tank, followed immediately by 1.7-g spherical RDX assemblies detonated outside the tank. Compared to mock-treated slice cultures, 1-3 consecutive RDX blasts caused progressive reductions in the synaptic proteins synaptophysin, GluR1, and NCAM-180 as determined by immunoblotting. Evidence that multiple blasts disrupt plasticity-related signaling (NMDA receptor-cofilin pathway) was also found. Note that the degree of synaptic decline correlated with increased HDAC2 measures, a histone deacetylase implicated in stress-induced loss of glutamatergic transmission and memory deficits. While DAPI staining was unchanged by the RDX-mediated blasts, punctate staining of synaptophysin and GluR1 was reduced in the

dendritic fields of the molecular layer and the stratum radiatum. Similar synaptic staining with an anti-NCAM monoclonal antibody, one that specifically labels the 180-kDa isoform, was also reduced. Interestingly, of the three synaptic markers, only GluR1 was found to be accumulated in the cell bodies of pyramidal neurons proximal to the dendritic fields exhibiting reduced synaptic marker staining. Thus, the level of explosive blasts used in the slice model appears to produce a unique type of pathology comprised of altered synaptic integrity before cellular deterioration, along with an apparent disruption of GluR1 transport. The selective synaptic pathology may explain the behavioral changes evident in some blast-induced TBI sufferers that have no detectable neuropathology, and it may shed light on how exposure to military blasts may influence the risk to dementia. Therapeutic avenues may need to promote the activity of compromised networks in the dentate gyrus and in CA1's stratum radiatum. Support: This material is based upon work primarily supported by the U.S. Army Research Laboratory and the U.S. Army Research Office under grant W911NF-14-2-0087, and partly by NIH grant 5R25GM077634-04.

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Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: NSFC, 81371306

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NSFC 81471332

Title: PTEN Inhibition improves white matter reparation after traumatic brain injury via activating Akt/mTOR pathway

Authors: X. JIANG[1,2], *Y. GAO[1,2], *Y. GAO[1,2], G. WANG[1], X. GAO[1], W. CAI[2], W. ZHANG[1], J. CHEN[1,2]
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Abstract: Aims: White matter injury, including axon and myelin damage, occurs in most of clinical traumatic brain injury (TBI) patients and usually leads to long-term neurological deficits.

However, most of the studies on TBI pay little attention on white matter reparation. Inhibiting phosphatase and tensin homolog deleted on chromosome 10 (PTEN) has been identified to enhance axon regeneration after spinal cord injury. Bisperoxovanadium(pic) (bpV(pic), which is a specific inhibitor for PTEN, may be a promising candidate to promote white matter restoration in brain injury. The aim of the present study is to test the role of bpV(pic) in white matter protection in experimental TBI.
Methods: Adult male C57BL/6J mice were subjected to controlled cortical impact (CCI) and then randomly assigned to vehicle and bpV(pic) treatment group. Mice without cortical impact were assigned to sham group. bpV(pic) (0.4mg/kg dilute in 200ul saline) was *i.p.* injected immediately after injury and followed by 3 more injections with an interval of 3h. Mice in vehicle and sham group received *i.p.* injection of 200ul saline. Tissue loss, neurological deficits and white matter integrity were assessed up to 35days after CCI. The expression of Akt and mTOR were then semi-quantified by western blot and immunostaining. For in vitro studies, primary cultured OPCs were treated with 1uM bpV(pic), the function of bpV(pic) on OPCs cell viability after OGD and it role in promoting OPCs differentiation were analyzed.
Results: Our results showed that bpV(pic) treatment leads to marginal reduction in tissue loss (62.14±6.5% of vehicle group) at 35d after CCI and largely improves neurological function in hang wire, rotarod test (7d, short term) and catwalk test (35d, long term). Interestingly, bpV(pic) significantly preserved white matter integrity and functional conductivity as evidencd by 1) improved MBP protein expression, 2) attenuated myelin sheath impairment and 3) strengthened compound action potential. Mechanically, the downstream Akt/mTOR pathway is activated as revealed by increased expression of phospho-Akt and phosphor-mTOR. Meanwhile, *in vitro* studies suggested that bpV(pic) enhanced oligodendrocytes progenitor cells (OPCs) survival or differentiation into mature oligodendrocytes (OLs) thus to promote white matter reparation.
Conclusions: These results demonstrated that inhibiting PTEN by bpV(pic) facilitated white matter reparation after TBI by promoting OPCs survival and promoting oligodendrogenesis through activating Akt/mTOR pathway.
Key words: PTEN, TBI, oligodendrocytes, white matter;

Disclosures: **X. Jiang:** A. Employment/Salary (full or part-time):; Pittsburgh Institute of Brain Disorder & Recovery and Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, USA. **Y. Gao:** 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.; The research was also supported by the Chinese Natural Science Foundation grants 81529002, 81371306, 81571285, 81471332.. **Y. Gao:** None. **G. Wang:** None. **X. Gao:** None. **W. Cai:** None. **W. Zhang:** None. **J. Chen:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Program#/Poster#: 139.05/AA8

Topic: C.09. Brain Injury and Trauma

Support: NIH Grant 1R01AG042890 to GT

Title: Decreased synaptosomal insulin responsiveness in the hippocampus of traumatic brain injured rats

Authors: *W. FRANKLIN[1,2,3], G. TAGLIALATELA[1,3]
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Abstract: Alterations of insulin signaling in neurons have been linked to many disorders including Alzheimer's disease (AD). Decreased insulin signaling increases synaptic sensitivity to amyloid beta (Aβ), a toxic protein in AD, thus contributing to the cognitive decline that characterizes this neurodegenerative disorder. Traumatic brain injury (TBI) is a risk factor for later development of Alzheimer's disease (AD), although the mechanisms contributing to this increased risk are unknown. To look at whether decreased insulin responsiveness in TBI animals is playing a role in the synaptic vulnerability to AD pathology, we developed a method for studying the insulin responsiveness at the synaptic level. We isolate functional synaptosomes from fresh or frozen rodent brain tissue and expose them to insulin in the presence of ATP to detect insulin receptor (IR) activation. Using this method coupled to Western blot analysis, we were able to detect insulin-driven phosphorylation of the IR. After optimizing this method, we analyzed synaptosomal insulin responsiveness in the hippocampi of SHAM and TBI animals that underwent a lateral fluid percussion injury at acute (2 and 7 days post-injury), intermediate (28 days post-injury), and chronic (3 months post-injury) time-points. We were able to detect acute decrease in insulin responsiveness in the brain of rats after traumatic brain injury that extends to longer time points warranting further experiments looking at downstream elements, inhibitory factors, and addressing the mechanism of action putatively involving increased synaptic sensitivity to the damaging impact of Aβ. The results support the idea that synaptic insulin resistance that ensues after TBI may be a risk factor for later development of AD.

Disclosures: W. Franklin: None. **G. Taglialatela:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Support: HICHD Grant HD061963

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Title: Blocking hypocretin receptor 1 reverses acute cognitive deficits and chronic depression-like behavior following mild TBI in adolescent female rats

Authors: *D. LENGEL[1], L. L. KRAFJACK[2], R. A. ESPAÑA[3], R. RAGHUPATHI[2]
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Abstract: Mild traumatic brain injury (mTBI) has been estimated to affect more than 1.2 million people in the U.S. per year, and can result in significant cognitive, motor, and emotional impairments (Bazarian et. al., 2010) (Viola-Saltzman & Musleh, 2016). Although females constitute approximately 1 in 4 people diagnosed with TBI (Wagner et. al., 2007), the influence of sex in the pathophysiology of TBI is not well understood. Further, high school girls are reported to sustain more sports-related mTBIs than boys (Gessel et. al., 2007), and some clinical studies report poorer outcomes in females (Bazarian et. al., 2010). However, animal models of mTBI have focused primarily on males. In a model of adolescent mTBI developed in our lab, female but not male rats were transiently impaired in the novel object recognition (NOR) task 3 days after injury, and developed long-term depression-like behavior in the forced swim test (FST) arising 6 weeks after injury. Previous work has demonstrated a role of hypocretin (HCRT) in memory consolidation in the novel object recognition (NOR) test (Rolls et. al., 2010), and some studies have reported an increase in HCRT expression in the hypothalamus after TBI (Willie et. al., 2012). Thus, we sought to investigate the effects of mTBI on cognitive and emotional tasks in female and male rats, and the influence of hypocretin in these tasks. Male and Female Sprague-Dawley rats underwent either a closed head injury or sham surgery, and were evaluated using the novel object recognition (NOR) memory test at 3 days post-injury and the forced swim test (FST) at 6 week post injury. There was an acute increase in hypocretin expression in the hypothalamus and prelimbic cortex in injured female but not male rats, which coincided with memory deficits at 3 days post injury. In order to investigate the role of hypocretin, intraperitoneal injections of either hypocretin-1 receptor antagonist (SB334867) or vehicle were administered to female rats after injury or sham surgery. The antagonist reversed

memory impairments in injured rats, while vehicle-treated injured rats continued to show a memory impairment. Antagonist-treated Injured rats also had lower immobility times on the FST at 6 weeks compared with vehicle-treated injured rats, which showed a significant increase in immobility time compared with sham rats. Thus, our data suggests that adolescent female rats are more sensitive to alterations within hypocretin circuits after mTBI than males, which may contribute to the development of cognitive and emotional impairments after injury. Future investigation should include measuring changes in dopamine expression and activity after injury.

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Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.07/AA10

Topic: C.09. Brain Injury and Trauma

Support: NIH R01 NS091218

Title: Elucidating the molecular crosstalk between autophagy and neuroinflammation following traumatic brain injury

Authors: *N. U. HEGDEKAR, C. SARKAR, P. RAVISHANKAR, D. PHILKANA, M. M. LIPINSKI
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Abstract: Neuroinflammation and autophagy dysregulation have been implicated as key mediators of post- traumatic brain injury (TBI) neuronal cell loss and neurodegeneration, though little is known about the molecular interplay between these two processes. Following controlled cortical impact (CCI) in C57Bl/6 mice, we observed accumulation of autophagosomes and inhibition of autophagy flux specifically in the activated microglia/macrophages, suggesting a potential function in neuroinflammation. Our studies using transgenic Cx3Cr1-GFP microglial reporter mice confirm that autophagy impairment peaks in activated cells of the microglia/macrophage lineage at day 3 post-CCI and this autophagy flux blockage persists through day 7. We are now analyzing $CCR2^{RFP/+}$ reporter mice and CCR2- knockout mice to determine whether the cells accumulating autophagosomes post-TBI are activated resident microglia or infiltrating peripheral macrophages. We are also elucidating the post-TBI polarization status of activated microglia/macrophages and determining whether impaired autophagy modulates microglia/macrophage polarization. Following CCI in transgenic GFP-LC3 mice, both pro-inflammatory “M1-like” and neuroprotective “M2-like” markers are expressed in GFP-LC3+ activated microglia/macrophages, indicating a mixed transitional (Mtran) phenotype

in these activated cells. Our in vitro experiments in BV2 microglial cells demonstrated that inhibition of autophagy can potentiate pro-inflammatory activation induced by LPS treatment, suggesting that microglial polarization can be modulated by changes in autophagy flux. We hypothesize that changes in autophagy levels observed after injury in vivo could affect microglia/macrophage polarization after TBI. The findings could provide insights into the molecular crosstalk between post-TBI autophagy and neuroinflammation and furthermore, suggest future targets for therapeutic interventions.

Disclosures: **N.U. Hegdekar:** None. **C. Sarkar:** None. **P. Ravishankar:** None. **D. Philkana:** None. **M.M. Lipinski:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Program#/Poster#: 139.08/AA11

Topic: C.09. Brain Injury and Trauma

Support: R37/ HD059288

Title: Branched chain amino acids do not recovered diminished behavioral threat response following mild traumatic brain injury

Authors: *J. REGER[1,2], A. S. COHEN[4], H. METHENY[3]
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Abstract: Traumatic brain injury (TBI) often leads to debilitating cognitive impairments and emotional destabilization in patients. Within the brain, the amygdala is implicated specifically in the conscious and autonomic response to emotional stimuli, and therefore could contribute to the emotional dysregulation after TBI. Branched chain amino acids (BCAAs), as a potential dietary therapy, have previously been shown to mitigate injury-induced cognitive impairments. Here, we investigated the effect of BCAA treatment on amygdala-involved behavioral threat response following experimental TBI. Mice were randomly selected to receive either lateral fluid percussion injury (LFPI) or sham surgery, and 24 hours later were placed on BCAA treatment or water control continuously for seven days. After the seven-day period, mice underwent behavioral testing using a cued-fear conditioning paradigm. Mice were first placed in context A and presented with a series of light and tone pairings followed by a footshock. Twenty-four hours after exposure to context A, mice were placed in context B and presented with light and tone pairings only. Behavioral threat response was measured as percent time mouse exhibited freezing behavior in context B. LFPI mice showed a significant diminished behavioral threat

response in comparison to sham mice. Interestingly, no significant differences was seen in LFPI mice who had received BCAA treatment and sham surgery animals. Therefore, these data suggest that BCAA therapy may have an effect on amygdala-involved behaviors or underlying amygdala function. Future studies aim to further increase the sample sizes of the groups and study the implications of TBI on the amygdala as well as investigate whether our treatment mitigates these effects.

Disclosures: J. Reger: None. **A.S. Cohen:** None. **H. Metheny:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: HD059288

NS069629

Title: Post-traumatic neurodegeneration detected by Fluoro-Jade C staining with parallel comparison to APP immunostaining and silver impregnation staining

Authors: *G. XIONG[1], H. METHENY[1], A. S. COHEN[1,2]
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Abstract: Traumatic brain injury (TBI) is a leading cause of death and disability in adolescents and young adults. A significant pathological consequence of TBI is neurodegeneration in key structures including the hippocampus, demonstrated by neuronal loss and hippocampal dependent cognitive impairment. This degeneration may subsequently lead to chronic dementia present in Alzheimer’s or Parkinson’s diseases. In order to mitigate this pathological progression, a major effort has been made over the past decades to develop effective diagnostic techniques and more sensitive markers that can be used in early stage of TBI. In the present study, we adopted Fluoro-Jade C (FJC) staining to reveal neurodegeneration in the mouse hippocampus after lateral fluid percussion injury (lFPI). We found that FJC demonstrates degeneration in neuronal cell bodies and their dendritic arbors, but not in their axons or terminals as had previously been suggested. FJC-positive staining in the hippocampus emerges as early as 2 hours and disappears 48 hours after lFPI. Immunohistochemical staining with amyloid precursor protein (APP) reveals unique axonal alteration in the corpus callosum and fibria including beaded varicosities and single bulb, together with positive mossy fiber terminals adjacent to FJC-

stained granule cells. The major advantage of silver impregnation staining is to trace argyrophilic axons in the alveus and hippocampal commissurae, in addition to detecting degenerative cell bodies, dendrites and mossy fiber terminals. Alterations in axons and terminals revealed by APP and silver staining are present 2 hours and last up to at least 1 week after lFPI. The present study demonstrates that FJC staining is time sensitive and cellular domain specific. It is suggested that FJC should be used in conjunction with APP immunostaining to demonstrate acute degeneration. For later stages of TBI, APP immuno together with silver impregnation staining may be more powerful.

Disclosures: G. Xiong: None. **H. Metheny:** None. **A.S. Cohen:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Program#/Poster#: 139.10/AA13

Topic: C.09. Brain Injury and Trauma

Support: R37 HD059288

Title: Dietary branched chain amino acids improve dentate gyrus-mediated spatial pattern separation behavior after mild traumatic brain injury

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Abstract: The dentate gyrus is thought to contribute to spatial memory processing via pattern separation, the process of making similar, overlapping patterns of neural activity more distinct. After mild traumatic brain injury (mTBI), our laboratory has previously shown that pattern separation ability is impaired. Additionally, it has been observed that there is a significant reduction in the concentration of branched chain amino acids (BCAAs) in the hippocampus after mTBI, and dietary BCAA administration has been shown to mitigate injury-induced spatial memory deficits. Therefore, we hypothesized that dietary administration of BCAAs can restore pattern separation behavioral deficits after mTBI, as a specific component of spatial memory processing. Two days following lateral fluid percussion injury (LFPI) or sham surgery, mice were placed on dietary BCAAs, or normal drinking water as a control for five consecutive days. One week after LFPI, pattern separation behavior was assessed in a modified spatial object recognition task. In this task, mice must detect the subtle spatial change of one of three identical objects in their environment. The data demonstrate that LFPI mice cannot discriminate the object’s spatial change when compared to sham mice who performed the same task. However,

LFPI mice placed on BCAAs demonstrate improved pattern separation and scored comparably to control sham mice. These findings suggest that BCAA administration restores pattern separation ability after mTBI. While the exact mechanism by which BCAAs reinstate cognitive abilities is still unknown, these results indicate that BCAAs may target dentate gyrus function following injury.

Disclosures: S. Samuel: None. **H. Metheny:** None. **A.S. Cohen:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.11/AA14

Topic: C.09. Brain Injury and Trauma

Title: Response of neurons following mechanical stretch *In vitro*: Effect of strain rate

Authors: *A. DILEONARDI, C. A. GUNNARSSON
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Abstract: Traumatic brain injury is a function of both the primary insult that causes brain deformation and the resulting secondary injury that leads to neuronal degeneration and death. Data suggests that the brain is susceptible to both the strain and strain rate of the insult. To understand how altering the strain rate affects secondary injury, we stretched cultured-primary hippocampal neurons on silicone membranes using the Cell Injury Controller II. The 2D strain tensor of the membrane was characterized using digital image correlation (DIC) at three different pressures (23, 47 and 63 psi) and three different times to peak (25, 50 and 75 ms). Strains and maximum principal strain rates were obtained from these conditions, from which a correlation between the input pressure profiles and the strain response of the membrane could be determined. Hippocampi from day E18 rat embryos were harvested, cultured and subjected to a biaxial stretch of 10mm peak deformation at three different rates (3, 5 or $8s^{-1}$) 10-12 days in vitro. Cells from the center region of the membrane where radial and tangential strains were approximately equal were used for analysis. Structural damage to neurons was quantified using immunocytochemistry of microtubule-associated protein 2 and functional damage was evaluated using live-cell imaging to visualize changes in cellular transport.

Disclosures: A. DiLeonardi: None. **C.A. Gunnarsson:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Program#/Poster#: 139.12/AA15

Topic: C.09. Brain Injury and Trauma

Support: MOST105-2314-B-016-001-MY3

TSGH-C106-066

TSGH-C106-065

MAB-106-035

Title: Nicotine-induced conditional place preference (CPP) is affected by head injury; correlation with dopamine release in nucleus accumbens shell

Authors: *Y.-H. CHEN[1], B. J. HOFFER[2]
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Abstract: TBI is known to impact dopamine-mediated reward pathways, but the underlying mechanisms have not been established.
Methods: We tested nicotine-induced conditional place preference (CPP) in rats exposed to 6 PSI fluid percussion injury (FPI) with and without prior exposure to nicotine, and then used fast scan cyclic voltammetry to analyze dopamine release in the shell portion of nucleus accumbens (NAc). To determine the impact of brain injury on nicotine withdrawal, nicotine infusion was applied to the rats after 6Psi FPI. The effect of TBI on CPP after prior exposure to nicotine and abstinence from nicotine was also assessed.
Results: After TBI, dopamine release in the shell portion of NAc was reduced (Control vs. Sham vs. 6Psi: 107.0±28.12 vs. 95.60±23.83 vs. -18.33±28.97 sec, paired t test) and nicotine-induced CPP was abolished. Chronic nicotine pretreatment blunted nicotine-induced CPP in sham-injured rats (Control vs. pretreatment Nicotine: 107.0±28.12 vs. 79.33±25.68 sec, paired t test). In the absence of nicotine, TBI did not alter tonic DA release in the shell, which remained minimal, but dramatically attenuated phasic release. Nicotine exposure substantially increased tonic release in sham-injured animals but did not impact phasic release; after TBI, nicotine exposure produced less increase in tonic release but did increase phasic release, although not to the levels seen in sham-injured animals. DA release was significantly reduced by both TBI and nicotine exposure, and CPP was associated with an increase in both tonic and phasic DA release. The conditioned preference time was related not only to phasic dopamine release (r^2=0.4759, linear regression) but also to the difference between tonic and phasic dopamine levels (r^2=0.8639, linear

regression). Nicotine withdrawal symptoms and DA release were not affected by 6Psi FPI (Control + Saline-infusion vs. Control + Nic-infusion vs. 6 psi + Nic-infusion: 4.000±0.68313 vs. 16.000±1.591645 vs. 14.16667±0.8724168 scores, paired t test).
Conclusion: By suppressing dopamine release from the shell portion of NAc, TBI impairs nicotine-induced CPP, which may relate to nicotine mediated reward.
Key wards: Shell, nucleus accumbens, dopamine, nicotine, conditional place preference

Disclosures: Y. Chen: None. **B.J. Hoffer:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: This work was supported by R01NS067417 from the National Institute for Neurological Disorders and Stroke (NINDS)

Title: Apolipoprotein-E4 (APOE4) impairs BBB stabilization and closure following traumatic brain injury

Authors: *B. MAIN, S. VILLAPOL, S. SLOLEY, D. BARTON, K. STEFOS, M. BURNS
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Abstract: Background: Blood Brain Barrier (BBB) dysfunction occurs in human TBI patients, yet the molecular mechanisms underlying this pathology remain unclear. The APOE4 gene polymorphism is associated with unfavorable outcomes after TBI including prolonged coma, poor prognosis and enhanced risk of late-onset Alzheimer's disease. Recent evidence implicates APOE polymorphisms in regulating BBB integrity in an isoform dependent manner, via suppression of Cyclophilin A (CypA)-Matrix metallopeptidase-9 (MMP-9) signaling at the Neurovascular Unit (NVU); however, the contribution of apoE to TBI-induced BBB permeability has not been investigated. **Methods/Results:** Wildtype (C57Bl/6) and humanized APOE3/APOE4 targeted replacement mice were subject to a controlled cortical impact model of TBI, before NVU and BBB permeability responses characterized at 1, 3, 7, and 10 days post-injury. In wildtype mice, an inverse relationship between soluble apoE and BBB permeability is observed, such that BBB permeability decreases as apoE levels increase over time post-TBI (n=5, **p<0.01). In APOE3 and APOE4 mice, acute pericyte loss is observed in both genotypes; however, APOE4 mice exhibit delayed pericyte recruitment back to the ipsilateral cortex 7 days post-TBI (n=4-5, ***p<0.001). Furthermore, QPCR analysis of microvessels revealed increased MMP9 expression in APOE4 mice at 1, 3 and 7-days post-TBI (n=5-6, **p<0.01), in parallel with reduced expression of tight junction proteins Zonula Occludens-1, Occludin and Claudin-5

compared to APOE3 counterparts (n=5-6, *p<0.05). Significantly, at 10 days post-injury, BBB leakage remains in APOE4 but not APOE3 mice (n=4-5, **p<0.05), suggesting the E4 isoform impairs BBB stabilization following TBI. This prolonged elevation of BBB permeability in APOE4-TR mice may contribute to deleterious secondary injury processes and indeed T2-weighted MRI shows APOE4 mice have 78% increased lesion volume compared to APOE3-TR mice, 28-days post-injury (n=8-11, **p<0.01). **Conclusion:** These results identify the key role of APOE in mediating BBB permeability and stabilization following TBI. Future studies investigating genotype-specific therapies targeting the BBB may prove beneficial in improving outcomes after TBI.

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Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

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Title: Autophagy is dispensable for normal axonal maintenance but required in Wallerian degeneration

Authors: *Y. FANG, H. WANG, X. CAO, Z. WANG, Q. WANG, Y. FANG
IRCBC, SIOC, Chinese Acad. of Sci., Shanghai City, China

Abstract: Axon degeneration is a prominent feature of spinal cord injury and many human degenerative diseases. Studies of the Wallerian degeneration slow (Wld^S) mouse indicate that axon degeneration is an active process, however, the underlying mechanisms remain elusive. To understand the self-destruction program of axon degeneration, we have developed a novel model of nerve injury using the *Drosophila* wing. The fly wing is translucent, allowing us to highlight the axons using fluorescent proteins and to monitor axonal changes in response to traumatic injury and ageing in *live* flies.
In this study, we expressed mCherry-labeled Atg8a (an homologue of mammalian LC3) in the wing nerve to visualize and investigate autophagy *in vivo* during aging and upon acute injury.

Formation of Atg8a/LC3 puncta is widely used as an autophagosome marker (Klionsky et al., 2016). During normal aging, we found that the basal levels of axonal autophagy (evident by the formation of mCherry-Atg8a puncta) are low in general, even in aged flies. However, upon axotomy, there is a rapid and massive autophagy induction in the distal segment of the injured axons. The response can be seen as early as 1 hr after injury and persists for days until the axons start to degenerate.
The injury-induced autophagy requires the core ATG genes, as RNAi-knockdown of Atg12 or Atg17 almost completely abolishes this response. Interestingly, no spontaneous axon degeneration is observed with knockdown of the above ATG genes. This data indicates that maintenance of axonal integrity during normal aging does not require axonal autophagy, however, it may play a critical role when axons are injured or stressed such as under disease conditions.
Further investigation reveals that, although overexpression of Wld^S or Nmnat can block known early injury responses such as Ca^{2+} influx, MAPK pathway activation and mitochondrial malfunction and protect injured axons from degeneration, they cannot block the injury-induced axonal autophagy. This data suggests that the rapid induction of axonal autophagy may be an additional pathway that is activated upon axon injury and transduces the injury signal to the action of axon degeneration. Indeed, in a targeted screen for autophagy genes involved in axon degeneration, we identified an autophagy-related gene whose downregulation significantly delays injury-induced axon degeneration. The ongoing experiments are to understand the molecular mechanisms of this gene and axonal autophagy in transducing injury signals to axon degeneration.

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Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: SUNY Downstate Dean's Research Investment Initiative Award

The New York State Institute for Basic Research in Developmental Disabilities

Title: Changes in molecular mediators of synaptic excitation and inhibition following traumatic brain injury in rats

Authors: R. DUGUE[1], R. ZANCA[2], W. STEWART[1], H. B. MICHELSON[1], J. H. GOODMAN[3], P. A. SERRANO[2], *D. S. LING[1]

[1]Physiol. and Pharmacol., SUNY Downstate Med. Ctr. Col. of Med., Brooklyn, NY; [2]Dept of Psychology, Hunter Col. and City Univ. of New York, New York, NY; [3]Dept of Developmental Biol., The New York State Inst. for Basic Res. in Developmental Disabilities, Staten Island, NY

Abstract: Previously, we have shown that traumatic brain injury (TBI) using the controlled cortical impact (CCI) model in rats leads to posttraumatic epileptogenesis (PTE) characterized by evoked and spontaneous ictal-like discharges in neocortex. We have also found that timely, post-injury administration of the antiepileptic drug levetiracetam (LEV) can prevent or inhibit PTE after CCI injury. In this study, we examined the effect of CCI trauma on the expression of molecular mediators of synaptic inhibition and excitation, including glutamic acid decarboxylase (GAD, the synthetic enzyme for the inhibitory neurotransmitter GABA) and the glutamate receptor subunits GluA2 (AMPA) and GluN2B (NMDA). We also examined the effects of post-injury administration of LEV on the expression of these synaptic mediators. In this TBI model, rats were subjected to severe CCI trauma (2.0 mm depth). Randomly selected CCI-injured rats were given a single dose of LEV (150 mg/kg, i.p.) immediately after injury, while drug-control subjects received only the saline vehicle. Sham-injured controls were not subjected to CCI. Three weeks after injury, rats (n = 6 - 7 per group) were euthanized and their brains snap-frozen for western blot analysis. Hemispheres ipsilateral to the CCI site were evaluated for GluA2, GluN2B, and GAD levels. We found that cortical GAD levels in CCI-injured (drug-control) rats were significantly lower than those in sham-injured subjects ($p < 0.05$), consistent with a decrease in synaptic inhibition. Conversely, levels of GluA2 and GluN2B were significantly higher ($p < 0.05$), suggesting an increase in glutamatergic synaptic excitation. Preliminary analysis of LEV-treated, CCI-injured rats suggests that post-injury administration of LEV prevents the injury-induced increase in GluA2. These results are consistent with the findings of our prior electrophysiological studies of TBI which showed that cortical trauma gives rise to a shift in the excitation-inhibition balance that produces heightened synaptic excitation and epileptiform activity, which can be prevented by post-injury administration of LEV. Together, these findings may provide clues about the molecular changes induced by cortical TBI that give rise to PTE.

Disclosures: R. Dugue: None. **R. Zanca:** None. **W. Stewart:** None. **H.B. Michelson:** None. **J.H. Goodman:** None. **P.A. Serrano:** None. **D.S. Ling:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: NIH

State of Indiana

Eli Lilly-Stark Neurosciences Research Institute Pre-Doctoral Fellowship in Neurodegeneration

Title: Acrolein following mild-blast traumatic brain injury contributes to parkinson's disease-like neuropathology

Authors: *G. G. ACOSTA[1], N. RACE[2,4], R. SHI[3]
[1]Basic Med. Sci., [2]Weldon Sch. of Biomed. Engin., [3]Depat. Basic Med. Sci., Purdue Univ., West Lafayette, IN; [4]Sch. of Med., Indiana Univ., Indianapolis, IN

Abstract: Blast-induced traumatic brain injury (bTBI) has led to a growing incidence of long-term neurological deficits among military service members and veterans. Particularly, combat-deployed veterans, exposed routinely to blasts in training and combat, have higher susceptibility to Parkinson's disease (PD) compared to age-matched non-combat service members. PD is characterized by α-synuclein protein-rich inclusions (Lewy bodies) and the progressive degeneration of nigrostriatal dopaminergic neurons; however, preclinical studies interrogating PD-related pathological changes in the brain after bTBI have not been performed. This study evaluates biochemical changes in the brain of mild bTBI rodent model, mimicking the signature injury of modern combat that are known to be linked to PD. With this approach, we aim to establish key intersections between bTBI and PD pathophysiology, which could help explain the increased rates of PD in combat Veterans. Specifically, we have focused on tyrosine hydroxylase (TH), α-synuclein, both known pathologies of PD, and acrolein, aiming to explore the synergies of bTBI and PD pathophysiology. We have shown that acrolein, a highly reactive aldehyde species with known pro-oxidative-stress and pro-inflammatory effects, persists up to a week following mild bTBI. Additionally, we have noted that acrolein may be a major contributing factor to the dysregulation of TH and α-synuclein protein aberrations after mild bTBI. Our data suggest acrolein and its pathological effects, particularly protein modification, are likely points of convergence between mild bTBI and PD. Acrolein and related reactive aldehydes could play a major disease-modifying role contributing to the higher incidence of PD in combat veterans. These results are expected to advance our understanding of the long-term consequences of blast-related injuries leading to the development of PD. Such efforts could eventually lead to the establishment of biomarkers for earlier diagnosis, or prevention/treatment to curtail the elevated incidence of post-bTBI PD.

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Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: StAAR Grant Dept. of Anesthesiology

Title: Fatty acid oxidation is increased following TBI in immature rat model of pediatric TBI

Authors: *S. SCAFIDI[1], C. BOWMAN[2], M. POUDEL[1], M. WOLFGANG[2]
[1]Anesthesiol. and Critical Care Med., Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [2]Biol. Chem., Johns Hopkins Univ. SOM, Baltimore, MD

Abstract: Traumatic brain injury (TBI) is the leading cause of permanent life-long disability in children and is characterized by deficits in learning and memory, cognition, attention and sensory-motor integration. Metabolic crisis caused by impaired oxidative glucose metabolism following TBI further contributes to cell death. Although glucose is the primary substrate for brain energy and metabolism, brain is also equipped with the ability to oxidize fatty acids for energy and metabolism. This study aimed to examine alterations in both brain glucose and fatty acid metabolism after TBI. Postnatal day 21-22 male rats were anesthetized with isoflurane and TBI was administered using a controlled cortical impact to the left parietal cortex. Harvested brains were dissected into ipsilateral cortex, ipsilateral hippocampus, contralateral cortex, and hippocampus. Using RT-PCR (Qiagen) we analyzed the expression of genes involved in regulation and enzymatic pathways of glucose and glycogen metabolism, as well as genes involved in fatty acid transport and metabolism at 24 hr, 72 hr and 7days after TBI. We found that both astrocytic (Glut1) and neuronal (Glut3) transporters RNA were peaked at 24hrs in all regions studied, while RNA for pyruvate dehydrogenase E1alpha - a key enzyme, which links glycolysis and Kreb's cycle, was decreased at 24hrs and 72hrs post injury. In contrast, Fabp7 (brain specific fatty acid transporter) was increased following TBI and peaked at 72hrs, while mitochondrial fatty acid metabolism genes (CPT1A, CPT2) were not changed after TBI. To determine the function, we measured glucose and fatty acid oxidation. Glucose oxidation was significantly decreased in ipsilateral cortex and hippocampus, while fatty acid oxidation was increased after TBI in the ipsilateral hippocampus but not in the cortex. This study provides evidence that brain following TBI is capable to use endogenous substrates (fatty acids) to meet the metabolic demands.

Disclosures: S. Scafidi: None. **C. Bowman:** None. **M. Poudel:** None. **M. Wolfgang:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Program#/Poster#: 139.18/AA21

Topic: C.09. Brain Injury and Trauma

Support: Sanford School of Medicine Faculty Research Grant

Center for Brain and Behavioral Research Trainee Research Grant

University of South Dakota Graduate Research Grant

Title: Effects of mild traumatic brain injury on GABA-A receptors and serotonin transporters differ between male and naturally-cycling female rats

Authors: *L. C. FOX, G. L. FORSTER
Univ. of South Dakota, Vermillion, SD

Abstract: Mild traumatic brain injuries (mild TBIs) make up over three quarters of head traumas in the United States yearly, and often occur in settings of stress (sports, warfare, domestic violence, etc.). Symptoms can persist for weeks, months or even years in some victims, and may include memory difficulties, mood changes, and frequently generalized anxiety. Both males and females are at risk for mild TBI, but differential outcomes have been observed between males and females. Males are more likely to receive a mild TBI, but a greater percentage of females complain of long term psychological complications. This study employed a rat model to examine potential mechanisms behind this sex difference. Male and naturally-cycling female adult rats received a mild TBI via a weight drop immediately following an episode of social defeat. Fixed brains were taken from males and from females in proestrus and diestrus phase on the day of fixation (at the extremes of ovarian sex steroid levels). Sections were labeled using immunocytochemistry for GABA-A alpha-1 receptor subunits, and for serotonin transporters (SERT), with NeuN as a neuronal marker. Staining intensities were then quantified using ImageJ software (from NIH). These neurotransmitters are known to be influenced by changes both in estradiol and progesterone levels. The hippocampus (CA1, CA3, and dentate gyrus (DG)) and the amygdala (basolateral (BLA), central (CeA), and medial (MeA) nuclei) were examined, as changes in these regions have been documented following mild TBI in this model, and both areas are involved with generalized anxiety behavior. It was found that mild TBI produced changes in GABA-A alpha-1 subunit expression in both sexes in the MeA, the BLA, and in CA1 of the hippocampus, with increases observed in males and proestrus females while mild TBI produced decreased GABA-A alpha-1 subunit expression in these regions. Mild TBI appeared to have few effects on SERT in either males or females, but intensity of SERT expression was sensitive to both sex and cycle phase. Our findings suggest that mild TBI-induced fluctuations in GABA-A receptor expression within sub-regions of the hippocampus and amygdala may influence post-injury symptoms between males and females. Furthermore, these findings suggest that responses to current therapies for these symptoms, such as SSRIs, may have different efficacy at the same dose in males versus females due to hormone-dependent differences in SERT expression.

Disclosures: L.C. Fox: None. **G.L. Forster:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: The Moody Project for Translational Traumatic Brain Injury Research

Title: Modulation of adult neurogenesis by Nano-Pulsed Laser Therapy in a rat model of traumatic brain injury

Authors: *E. MOCCIARO[1,4], R. ESENALIEV[2,3], I. PETROV[2], Y. PETROV[2], M. O. PARSLEY[1], K. M. JOHNSON[1], I. J. BOLDING[1], A. UNTEREINER[1], C. SZABO[1], D. S. PROUGH[1], M. MICCI[1]
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Abstract: Background: Traumatic Brain Injury (TBI) is a chronic disease that occurs after a head trauma. One of the brain regions most affected by TBI is the hippocampus, which plays a pivotal role in learning and memory and is one of the only two regions in the brain where neurogenesis occurs throughout life. We have previously shown that transcranial delivery of Nano-Pulsed Laser Therapy (NPLT), that combines near-infrared laser light (NIL; 808 nm) and laser-generated, low-energy optoacoustic waves (OAW), is neuroprotective in rats with blast-induced neurotrauma. Here we tested the ability of NPLT to modulate hippocampal neurogenesis in rat fluid percussion injury (FPI) TBI. **Methods** Adult male rats were treated with NPLT 1 hour after FPI or sham surgery. Proliferation of neural stem cells (NSC) in the hippocampus was studied using BrdU incorporation 2 weeks later. *In vitro*, we analyzed the effect of the main components of NPLT, NIL and OAW, on the proliferation (EdU uptake) and differentiation (immunofluorescence) of NSC isolated from adult rat hippocampus (hipp-NSC). The expression of miRNAs known to regulate neurogenesis and mitochondrial bioenergetics (known to play a critical role in the regulation of stem cell differentiation) were also assessed (qRT-PCR and Seahorse assay). **Results:** NPLT stimulated NSC proliferation in the hippocampus of uninjured rats and prevented their aberrant proliferation induced by FPI. *In vitro*, OAW and NIL+OAW increased Hipp-NSC proliferation, while NIL alone did not. NIL+OAW also increased the expression of miR9, mir25, and miR29 (known to stimulate proliferation), while OAW treatment decreased their expression. Both NIL+OAW and NIL treatments stimulated mitochondrial bioenergetic in hipp-NSC. **Conclusions**: NPLT selectively regulates neurogenesis by modulating the expression of specific miRNAs and by stimulating mitochondrial bioenergetic.

Disclosures: **E. Mocciaro:** None. **R. Esenaliev:** None. **I. Petrov:** None. **Y. Petrov:** None. **M.O. Parsley:** None. **K.M. Johnson:** None. **I.J. Bolding:** None. **A. Untereiner:** None. **C. Szabo:** None. **D.S. Prough:** None. **M. Micci:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.20/AA23

Topic: C.09. Brain Injury and Trauma

Support: NCTR protocol E7584.11

Title: Traumatic brain injury induces cell death and alters IGF signaling in human primary dopaminergic neuronal precursor cells

Authors: *H. ROSAS-HERNANDEZ[1,2], S. M. LANTZ[2], E. CUEVAS[2], M. G. PAULE[2], S. Z. IMAM[2], S. F. ALI[2]
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Abstract: Traumatic brain injury (TBI) is caused when an external mechanical force induces damage to the brain, resulting in tissue deformation. Although one of the consequences of TBI is neuronal cell death, different molecular mechanisms are triggered in response to the initial trauma that can affect the outcome of recovery, including insulin-like growth factor-1 (IGF-1) signaling. IGF-1 is a polypeptide hormone with a wide variety of functions in brain including: cell proliferation and survival, axon myelination, and neurite outgrowth. Although IGF-1 is synthetized mainly in the liver under the influence of growth hormone (GH), IGF-1 can also be locally produced in the brain by a GH-independent mechanism. Serum levels of IGF-1 are decreased after brain injury, probably due to pituitary dysfunction, whereas brain levels of IGF-1increase after TBI. Exogenous administration of IGF-1 has been shown to induce neuroprotection after TBI. Therefore, the aim of this study was to evaluate, in vitro, whether neuronal levels of IGF-1 and related proteins are modified after TBI. Human primary dopaminergic neuronal precursor cells (HPDNPCs) were differentiated in culture for 7 days before being submitted to mild (10% stretch) or severe (50% stretch) TBI using a commercially available system and subsequent analyses were performed 1 and 7 days after stretch injury. Release of lactate dehydrogenase (LDH) served as an index of cell death and levels of IGF-1, IGF-2, insulin and IGF binding proteins (IGFBPs) were measured in cell lysates using an IGF signaling array. LDH release increased only after 50% stretch 1 day post-injury and returned to control levels after 7 days. 50% stretch decreased while 10% stretch increased IGF-1 levels 1 day post injury; however the levels of this hormone were decreased under both conditions after 7 days. IGF-2 decreased 1 day after injury and increased after 7 days under both conditions.

IGFBPs remained essentially unchanged, except for IGFBP-2, which increased after 10% and 50% stretch and both 1 and 7 days post injury. On the other hand, insulin levels decreased 1 day post injury under both conditions, whereas 10% decreased and 50% increased insulin levels 7 days after injury. These data suggest that IGF signaling is altered by both mild and severe TBI and may trigger different mechanisms inside the neuron independent of cell death since the proteins involved in IGF signaling were differentially expressed in conditions in which no cell death was observed. Further investigation is required to identify which neuronal functions are altered by IGF signaling after TBI and if manipulation of associated pathways might confer neuroprotection after brain injury.

Disclosures: H. Rosas-Hernandez: None. **S.M. Lantz:** None. **E. Cuevas:** None. **M.G. Paule:** None. **S.Z. Imam:** None. **S.F. Ali:** None.

Poster

139. Brain Injury: Cellular Mechanisms

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Topic: C.09. Brain Injury and Trauma

Support: US_Army_CCCRP_H_026_2014_WRAIR

US_Army_CCCRP_H_008_2017_WRAIR

Title: Changes in neuroplasticity responses following penetrating ballistic-like brain injury in adult rats

Authors: *S. KIZHAKKE MADATHIL, Y. DENG-BRYANT, B. WILFRED, S. URANKAR, T. LALA, X. YANG, J. GILSDORF, S. DEBORAH
WRAIR, Silver Spring, MD

Abstract: Cognitive impairment is one of the chronic effects of traumatic brain injury on its survivors. Despite years of research, molecular events leading to these behavioral deficits are poorly known. Abnormal or inadequate neuroplasticity responses are presumed to play a role in the development of post-traumatic behavioral defects. To design strategies that promote neurorepair, we need to understand the changes in post-traumatic neuroplasticity. Here we examined the effects of penetrating ballistic-like brain injury (PBBI) on synaptic plasticity and neurogenesis. Changes in synaptic plasticity were determined using synaptophysin and GAP-43 western blots. To study neurogenesis, immature neuronal population was quantified from two major neurogenic niches of the adult brain viz., sub-ventricular zone (SVZ) and sub-granular zone (SGZ). Synpatophysin and GAP-43 protein levels were quantified in both hippocampal and cortical homogenates (n=4 PBBI, 2 sham) at different time points (1-14d). To capture

proliferating cells, rats were injected with BrdU for 7 days and were euthanized at 10 day post-injury (n=6 PBBI, 6 sham). Doublecortin (DCX) immunolabeling was used to identify immature neurons and BrdU/DCX double-labelling was performed to identify newborn immature neurons. To understand forebrain neurogenesis, total DCX neurons and BrdU positive DCX neurons were counted separately in SVZ, striatum, subcortical white matter (SCWM) and cortex. In the hippocampus, DCX and Brdu/DCX co-labelled cells were counted from SGZ. While cortex showed a reduction in synaptic plasticity, GAP-43 levels were increased in the hippocampus at 1 and 14d ($p<0.05$) after injury, indicating initiation of neuroreparative changes. DCX positive neurons and BrdU/DCX co-labelled newborn immature neurons were found in both SVZ and SGZ, regardless of the injury status. However, PBBI appeared to enhance the production of newborn neurons in both SVZ and SGZ areas. Furthermore, PBBI significantly enhanced the migration of newborn neurons from SVZ towards striatum, SCWM and cortex ($p<0.05$ compared to sham). In the hippocampal SGZ, PBBI did not alter the total number immature neurons however, increased the number of BrdU/DCX co-labelled newborn neurons ($p<0.05$ compared to sham). Overall, our results indicate changes in synaptic plasticity and an activation of neurogenesis in two major neurogenic niches of the adult rat brain following PBBI. Our findings also show that these newborn neurons can migrate to areas of injury, purportedly to modulate neurorepair. Further studies will characterize the anatomical integration of newborn neurons and their role in mediating functional recovery.

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Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.22/AA25

Topic: C.09. Brain Injury and Trauma

Title: Nuclear rotations in nerve cells after tangential impact trauma *In vitro* are associated with large, long lasting changes in network electrophysiological activity

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Abstract: We have previously demonstrated [1,2] that rapid acceleration (impact) exposure of neuronal networks on micro electrode arrays results in reproducible changes in spontaneous activity that can be described in terms of two phases: An initial activity depression that is almost reversed in approx. 1 hour (Phase 1), and a subsequent slow decrease to persistent levels 30 to 40% below reference (Phase 2) that last at least 48 hours. A ballistic pendulum was selected for impact generation to produce repeatable tangential accelerations. A stainless steel chamber was

completely filled with medium to prevent medium movement and eliminate hydrodynamic stress. We are now reporting delayed nuclear rotations after impact and extensive cross correlation profile changes. Strong cell substrate adhesion of dissociated cortical tissue remains stable during and after impact. Five successive 400g impacts in a window of twenty seconds resulted in nearly 100% observations of nuclear rotation as judged by movement of the nucleolus. Rotations appear to occur primarily in the horizontal plane. Such nuclear movement is not immediate, but starts with small oscillations after a delay of ten to thirty minutes, followed by rotation at rates ranging from 20-60 deg per hour. Major rotations stop in 5-6 hours. These morphological observations are associated with functional, electrophysiological changes. Analysis of cross correlations (CC) from wave shape identified units show impact-related alterations of spike distribution profiles, frequency, and network oscillations. Phase 1 is associated with a general dampening of oscillation amplitudes and with profile changes that often show reversal of CC peaks, reflecting revision in firing hierarchies. Oscillation frequencies of most units remain stable at 2.4 - 2.7 Hz, although increases to 3.5 Hz have been noted. Phase 2 (starting about two hours after impact) is dominated by a greater decrease in oscillation amplitudes and loss of network oscillation on some channels. Networks disinhibited with bicuculline show expected lower oscillations (reflecting population bursts, ~0.5 Hz) but show drastic (50%) decreases in oscillation amplitudes and a 20% decrease in frequency. The data support the hypothesis that nuclear rotation and associated protein trafficking disruption affect synapse function and cell-cell communication.

[1] Smith DC, Gross GW (2014) Proceedings, 9th International MEA Meeting. 156-157. DOI: 10.13140/RG.2.1.4395.
[2] Rogers EA, Gross GW (2016) Society for Neuroscience Abstract #2905

Disclosures: E.A. Rogers: None. **G. Gross:** None.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: NIH Grant 1 U44 NS090616

Azevan Pharmaceuticals, Inc.

Title: Treatment of repetitive, mild traumatic brain injury (rmTBI) with a highly selective, orally active arginine vasopressin V1a receptor antagonist

Authors: *N. G. SIMON[1], P. KULKARNI[4], T. MORRISON[4], S.-F. LU[6], A. SIDWELL[2], S. O'NEAL[3], C. F. FERRIS[5]

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Abstract: Arginine vasopressin (AVP) is a chemical signal in the brain influencing cerebral vascular resistance and brain water permeability and contributes to the pathophysiology of brain edema following head trauma. These cerebrovascular effects are mediated through the AVP V1a receptor, which is highly expressed in cortical and subcortical brain areas across all mammals. To study the therapeutic potential of AVN576, a selective V1a antagonist, on rmTBI we adopted the momentum exchange model developed by Viano and colleagues to mimic concussions found in the National Football League. This model features several translational advantages over similar models. For example, the head, neck and body can move with impact, and the velocity of head movement and energy transfer can be calculated and scaled to reflect a mild concussion in humans without mortalities, skull fractures, or contusions. Male Sprague Dawley rats were concussed three times with one day between. Drug (n = 5) and vehicle (n = 5) were given immediately after each mild concussion. Non-concussed rats (n=6) served as controls. At one and six weeks post-concussion all animals were scored for cognitive (Barnes maze, novel recognition), motor (beam walk and rotarod) and emotional (elevated plus maze) behaviors. Concussed, vehicle-treated animals showed longer lasting deficits in cognition and emotion as compared to control and AVN576 treated animals. Rats were also imaged in a Bruker 7.0T scanner 1, 14 and 42 days following final impact using protocols to assess capillary density (QUTE-CE), gray matter microarchitecture (DWI), edema (T2 relaxivity) and functional connectivity (resting state BOLD). All images for each modality were registered to a 3D MRI rat atlas to assess neurobiological differences between groups across 171 brain areas. Acutely, AVN576-treated and concussed vehicle-treated animals showed similar signs of inflammation and white matter damage. These deficits were reduced, however, over the long term in drug-treated animals while the concussed vehicle group showed altered patterns of functional connectivity and indices of anisotropy primarily localized to the hindbrain and amygdala.

Disclosures: **N.G. Simon:** A. Employment/Salary (full or part-time):; Azevan Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Azevan Pharmaceuticals, Inc. **P. Kulkarni:** None. **T. Morrison:** None. **S. Lu:** A. Employment/Salary (full or part-time):; Azevan Pharmaceuticals, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Azevan Pharmaceuticals, Inc.. **A. Sidwell:** None. **S. O'Neal:** None. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.24/AA27

Topic: C.09. Brain Injury and Trauma

Title: Life without a brain and the wonders of neuroplasticity: Rat 222

Authors: *C. F. FERRIS[1], X. CAI[1], P. KULKARNI[1], T. MORRISON[1], J. QIAO[1], S. IRIAH[1], S. MALMBERG[1], L. TIMMS[1], K. SINKEVICIUS[2], J. BAUN[3], J. BALLARD[3], T. YORK[3], B. SWITZER[3]
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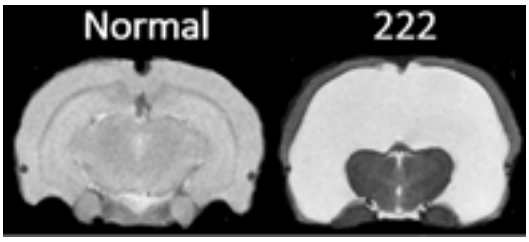
Abstract: In an era where magnetic resonance imaging (MRI) is common place around the world, more and more cases of extreme alterations in brain morphology appear in the literature (Lancet 2007: 370:262) and popular press. Usually caused by early hydrocephalus, large regions of the brain can be absent. Nonetheless, if this transformation occurs early enough in development the affected individuals can lead a normal life, without any apparent sensory/motor, cognitive or emotional deficits. The localization of function to specific areas of the central nervous system is a fundamental axiom of developmental neurobiology across the mammalian kingdom. However, when forced to redraft nature's plan due to severe limitations in space, as shown in the figure, how does the brain reorganize itself?
Numerous MRI modalities (e.g. BOLD, DWI, angiography, T2/T1 and functional connectivity) were used to characterize brain function and morphology in RNASET2 knock out rats from ages 3 months to 2 years. One of the 2 years old animals, rat 222, was missing over 85% of its brain. Its general health and body weigh did not differ from wild-type and other KO rats of similar age. When tested for motor behavior and spatial memory, there were no significant differences from age matched rats despite the absence of the hippocampus and much of the basal ganglia. R-222 could see and hear in the absence of the auditory and visual cortices. A ribbon of cortex, in what would be identified as motor and somatosensory, existed but showed little if any evoked activity to foot shock; instead, the brain stem showed activity patterns that matched the timing of the foot shock. The only recognizable brain areas in R-222 were olfactory bulb and adjacent prefrontal cortex and brainstem. Resting-state functional connectivity suggested a separate organization between the forebrain and brainstem. In collaboration with NeuroScience Associates, the neurochemical organization of R-222 was studied helping to characterize the distribution of dopamine, norepinephrine and acetylcholine.



Disclosures: **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research. **X. Cai:** None. **P. Kulkarni:** None. **T. Morrison:** None. **J. Qiao:** None. **S. Iriah:** None. **S. Malmberg:** None. **L. Timms:** None. **K. Sinkevicius:** None. **J. Baun:** None. **J. Ballard:** None. **T. York:** None. **B. Switzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuroscience Associates.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.25/AA28

Topic: C.09. Brain Injury and Trauma

Support: LQ1605 from the National Program of Sustainability II (MEYS CR)

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

Title: Real-time analysis of axonal swellings development

Authors: *V. M. POZO DEVOTO, V. LACOVICH, M. CARNA, M. FEOLE, K. TEXLOVA, G. B. STOKIN
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Abstract: Axonal swellings (AxS) are focal enlargements of axons found in post-mortem brains of patients with neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease and Amyotrophic Lateral Sclerosis or Traumatic Brain Injury. Despite their description in a wide range of biological and pathological settings, the mechanisms underlying AxS development, the consequences for axonal homeostasis and the relationship of AxS to reversible correction of axonal dysfunction remain poorly understood. Here, using human stem cells derived neurons, we develop an in vitro experimental approach that allows the study of real time axonal structural changes and assessment of molecular mechanisms underlying AxS formation.
Human neuronal progenitor cells were seeded in specifically designed microfluidic chambers, and terminally differentiated to neurons. In these chambers axons grow inside channels, which

are interrupted by one perpendicular channel connected to a syringe pump. A full characterization of the channel fluid dynamics under different pump flows was conducted. To test the axonal response to a mild but sustained flow, we transduced neuronal cultures with lentiviral vectors carrying a modified Cherry that targets cellular membranes. Time-lapse movies of neurons were acquired to assess membrane changes during injury. Detailed analysis of the kinetics during and after injury show a significant increase in the number and size of axonal enlargements, featuring a particular shape and periodicity in the axonal segment subjected to injury. Furthermore, simultaneous incubation with a Ca++ sensor probe revealed a significant increase in Ca++ concentrations in the sites of the enlargement formation, suggesting a relevant role for Ca++ in AxS formation. In addition axonal cytoskeletal changes were analyzed after injury by super-resolution microscopy. Changes in the distribution and periodicity of structural proteins such as Spectrin βII and neurofilaments were found.
This model represents a huge step for real time analysis of AxS formation, allowing not only the study of structural modification of axonal integrity during and after injury, but also of the molecular events involved in AxS development.

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

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.26/DP05/AA29 (Dynamic Poster)

Topic: C.09. Brain Injury and Trauma

Title: The long-term neurobiological and behavioral consequences of repetitive, mild traumatic brain injury (rmTBI): A multimodal MRI study in rats

Authors: *P. P. KULKARNI[1], T. MORRISON[1], X. CAI[2], J. QIAO[3], S. IRIAH[4], L. NEUROTH[4], C. F. FERRIS[5]
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Abstract: The objective of this study was to develop an animal model of early rmTBI that could be used to follow future risk for neurodegenerative diseases (e.g. Parkinson's and Alzheimer's) in aging rats. To this end, we adopted the momentum exchange model developed by Viano and colleagues to mimic concussions found in the National Football League. This model features several translational advantages over similar models. For example, the head, neck and body can move with impact, and the velocity of head movement and energy transfer can be calculated and scaled to reflect a mild concussion in humans without mortalities, skull fractures, or contusions.

Male Sprague Dawley rats were concussed 1, 3, or 5 times with one day between. Non-concussed rats served as controls. Six weeks post-concussion, rats were scored for cognitive (Barnes maze, novel recognition), motor (beam walk and rotarod) and emotional (elevated plus maze) behaviors. Rats concussed 5 times showed major deficit in all of these behavioral measures, while those exposed to 1 and 3 concussions showed no deficits in cognitive or motor tasks but changes in anxiety as compared to controls. Rats were also imaged in a Bruker 7T scanner to assess capillary density (QUTE-CE), gray matter microarchitecture (DWI), edema (T2 relaxivity) and functional connectivity (resting state BOLD). All images for each modality were registered to a 3D MRI rat atlas to assess neurobiological differences between groups across 172 brain areas. Rats concussed 3 times showed significant alterations in all imaging modalities primarily localized to brainstem, amygdala and hippocampus

Disclosures: P.P. Kulkarni: None. **T. Morrison:** None. **X. Cai:** None. **J. Qiao:** None. **S. Iriah:** None. **L. Neuroth:** None. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Animal Imaging Research.

Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.27/AA30

Topic: C.09. Brain Injury and Trauma

Support: NCAA Mind Matters

Fordham University Faculty Research Grant

Title: The effect of sub-concussion impacts on post-exercise memory performance

Authors: *D. D. LEEDS[1], B. R. JOHNSON[2], D. DEFONTES[3], C. J. D'LAURO[4]
[1]Computer and Information Sci., Fordham Univ., Bronx, NY; [2]Behavioral Sci. and Leadership, U.S. Air Force Acad., Colorado Springs, CO; [3]Univ. of Notre Dame, Notre Dame, IN; [4]Dept. of Behavioral Sci., US Air Force Acad., USAF Academy, CO

Abstract: Sub-concussive head impacts - blows to the head that do not produce concussive symptoms - may increase risks for cognitive impairment. Careful study of motion during impacts, paired with cognitive testing, may reveal classes of motion particularly harmful to the brain.
Data Collection: We studied Air Force Academy volunteers who participated in either a boxing or swimming physical exercise. Before class, cadets were outfitted with a head acceleration monitoring device that recorded all impacts over 10 g’s. After class, they completed a

recognition memory experiment in which they were presented "target" words to encode in memory during study phase, and then attempted to identify these targets while rejecting "lures" during the test phase. Cadets completed two study-test cycles. A total of 63 cadets completed this task (25 boxing, 38 physical development).
Analysis: A set of summary statistic calculations represents the magnitude of head impacts. We evaluate several standard statistics - including Peak Linear Acceleration (PLA) and Head Impact Criterion (HIC)-30 ms - and new statistics derived by Principal Component Analysis (PCA) from typical head motion patterns during impacts. Critically, for each statistic, we find the correlations between impact magnitude and post-exercise memory.
Results: Using PCA, we identify ten distinct 100-ms acceleration "principal component" (PC) patterns that account for over 90% of variance in boxing head motions during impacts. The most representative patterns (PCs 1, 2, and 3) focus on the initial rise and fall of linear acceleration in the first 10 ms after time of impact. We find the magnitude of motion corresponding to the first and third PCs (PC1 and PC3) shows strong negative correlation with boxing post-exercise memory performance (PC1: r=-0.35, PC3: r=-0.56). Traditional impact summary statistics similarly reveal a decrease in memory performance with increased impact magnitude, but with notably smaller correlations (HIC-30: r=-0.19, PLA: r=-0.05). PC correlation results for cadets in the physical development class are surprisingly opposite, with magnitude of PC1 and PC3 showing positive correlations with memory (r=0.13 and r=0.16 respectively). However, a strong negative correlation remains for both boxing and physical development when studying magnitude for PC7 (r=-0.15 for boxing and r=-0.34 for physical development), capturing after-shock accelerations in the 25-40 ms after initial impact.
Conclusions: Immediate (<20ms) impacts correlated with decreased memory performance for boxers, but not for non-boxers. Delayed impact components (25-40ms) showed negative memory correlations in both conditions.

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Poster

139. Brain Injury: Cellular Mechanisms

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 139.28/AA31

Topic: C.09. Brain Injury and Trauma

Support: NIH RO1 NS050465

NIH RO1 DK104363

Title: Extracellular matrix control of the TBI pathology: The role of fmod gene

Authors: *S. D. REGE[1], Z. YING[2], X. YANG[3], F. GOMEZ-PINILLA[4]
[1]Integrative biology and Physiol., [2]Dept of Integrative Biol. and Physiol., [4]Integrative Biol. and Physiol., [3]UCLA, Los Angeles, CA

Abstract: Traumatic Brain Injury (TBI) is a leading cause of mortality and permanent disability worldwide imposing enormous social and economic burden on society. It is imperative to tailor specific preventive measures to alleviate the escalation of this silent epidemic. Our previous systems biology study revealed Fibromodulin *(Fmod)* to be one of the key driver genes that controls a network of genes modulated by TBI. *Fmod*, a small leucine rich proteoglycan (SLRP) is an essential structural component of extracellular matrix (ECM) characterized by a protein core substituted covalently with glycosaminoglycan (GAG) chains. The biological actions of ECM genes are more pronounced in various tissues such as skin, tendon, liver, heart and kidney; however, little is known about the role of ECM genes in brain and TBI. Recently, ECM genes have attracted a great deal of attention for their crucial role in the regulation of neuronal function and synaptic plasticity. In the present study, we sought to examine the neuroprotective role of Fmod against the disruptive effects of TBI on cognition. Homozygous three months old male wild type (WT) and *Fmod* knockout (KO) mice were trained on the Barnes maze test for 5 days to learn the task, and were then exposed to Sham injury and Fluid Percussion Injury (1.6-1.8 atm) respectively. After one week of surgery, animals were subjected to Barnes maze task for memory retention analysis. Compared to Sham injured WT animals, TBI resulted in impaired memory. Interestingly, deletion of *Fmod* gene was found to exhibit protection against the detrimental effects of TBI. In addition, we further propose to unveil the molecular mechanisms mediating the action of *Fmod* against TBI on hypothalamic inflammation and behavior phenotypes. It is also interesting that *Fmod* has been found (Meng et al, EBiomedicine, 2016, 2017) to be the hub of a network of genes modulated by the consumption of the sugar fructose which suggests that *Fmod* can be central to metabolic perturbations carried by fructose and TBI. Our work was found to substantiate the role of proteoglycans in regulating gene networks implicated in cell communication, neuronal signaling and cognition, and will ensure a more targeted approach to combat various neurological and psychiatric disorders.

Disclosures: S.D. Rege: None. **Z. Ying:** None. **X. Yang:** None. **F. Gomez-Pinilla:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.01/AA32

Topic: C.09. Brain Injury and Trauma

Support: NIH/NINDS R01 NS030853 (RJN)

Title: Interhemispheric neuroanatomical connectivity following unilateral cortical injury

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Abstract: Following brain injury, neuronal plasticity in uninjured brain regions is a critical component in the recovery of motor function. While natural (spontaneous without therapeutic aid) functional motor recovery has been well documented, neuroanatomical changes underlying functional recovery are less understood. Our prior work in rodent and non-human primate models has documented an array of neuroanatomical changes in the spared cortical areas of the injured (ipsilesional) hemisphere. The role of the intact (contralesional) hemisphere in functional recovery is less clear. Recent non-invasive stimulation and neuroimaging studies have demonstrated changes in the contralesional hemisphere following cortical injury suggesting that the uninjured hemisphere plays a supportive role in recovery of motor function. The purpose of this study is to determine whether interhemispheric neuroanatomical connections between spared motor areas are altered following a unilateral cortical injury. Adult male Long-Evans rats were randomly assigned to two groups: 1) primary motor cortex (M1) lesion and 2) control (no lesion). Three weeks after an ischemic lesion in M1, a neuronal tract-tracer (10k MW biotinylated dextran amine, BDA) was injected in the ipsilesional premotor cortex (PM). Following a 7-day period for neuronal transport, animals were euthanized and the brains fixed. Cortical tissue was separated from underlying structures, flattened, sectioned tangential to the cortical surface, and stained to visualize BDA. Labeled synaptic boutons were quantified using unbiased stereological techniques to examine the spontaneous sprouting of ipsilesional PM fibers terminating in contralesional cortical regions. Preliminary data demonstrate interhemispheric connectivity to the contralesional PM in both lesion and control animals and suggest an increase in synaptic bouton density in the lesioned animals indicating reorganization of interhemispheric connections following an ischemic lesion. The increase in PM connectivity to the contralesional hemisphere may be an important piece of the overall neuroanatomical changes occurring in spared cortical areas that contribute to spontaneous recovery of motor function.

Disclosures: H.M. Hudson: None. **E.T. Urban:** None. **S. Barbay:** None. **R.J. Nudo:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.02/AA33

Topic: C.09. Brain Injury and Trauma

Support: Merit Review Award I01RX001144 from the U.S. Department of Veterans Affairs Rehabilitation Research and Development Service

Gordon Project of HMS and C.S.C. and U.W.S.F. fellowships

Title: Model of co-occurring mild traumatic brain injury and conditioned fear in mice that produces cognitive, behavioral and neuroinflammatory impacts

Authors: *G. B. KAPLAN[1], S. C. HEINRICHS[2], L. WANG[3], T. GLASER[3], K. A. LEITE-MORRIS[1], K. RUMBIKA[2], O. NGUYEN[2], Y. D. TENG[3]
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Abstract: The high rates of TBI and PTSD diagnoses encountered in recent years by the U.S. Veterans Affairs Healthcare System have increased public awareness and research investigation into these conditions. In this study, mild traumatic brain injury (mTBI) and posttraumatic stress disorder (PTSD) were modeled in male C57BL/6 mice in order to determine the co-morbid effects of mTBI and PTSD on cognition, behavior and neuroinflammation within 3 weeks of injury. We used fear conditioning (FC) as a behavioral test to model PTSD. In the FC model, the fear cues and contexts activate freezing behavior and recruit a similar neurocircuitry as seen in PTSD patients. The rodent fluid percussion injury (FPI) model produces focal and diffuse brain injury dependent on the intensity of force applied to a cortical site of injury. The FPI model has strong validity as it replicates the injury and behaviors of the human condition. FPI followed by FC (produced 1 week after FPI) were employed in this comorbid animal model. After only six fear conditioning sessions, the fear cues and contexts were shown to be aversive and produced near-complete immobility. There were five groups under study: naïve controls, FC/unoperated mice, FC/FPI 0.0 (sham controls), FC/FPI 0.7 atm, FC/FPI 1.7 atm. The novel object recognition test was used to examine recognition memory and was reduced in both fear and fear/FPI mouse groups relative to naïve controls. Re-exposure to the fear cue and context several days after fear acquisition showed the retention of immobility in all FC groups. Preliminary evidence shows differences in fear extinction among the FC groups. Following the completion of behavioral testing, brains were harvested to quantify inflammation and neuropathology in unoperated control mice as well as craniotomy sham surgery and FPI exposed groups. Immunohistochemical (IHC) staining of activated macrophage/microglia marker CD68, and pro-inflammatory marker TNF-α showed evidence of neuroinflammation in cortical, hippocampal and subcortical brain regions as a consequence of mTBI/FC. IHC staining of β-amyloid precursor protein was used as a measure of diffuse axonal injury and this biomarker was induced in cortical and subcortical regions. This FPI/FC mouse model shows translational efficacy as a model for mTBI/PTSD and produces subacute cognitive impairment and fear retention accompanied by neuroinflammation and axonal injury in cortical, subcortical and hippocampal regions. Ongoing studies will examine longer-term behavioral, neuroinflammatory, neuronal morphological effects in this mFPI/FC model and test possible treatment approaches.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.03/AA34

Topic: C.09. Brain Injury and Trauma

Support: Pre-Doctoral Fellowship from the New Jersey Commission on Brain Injury Repair

Title: Genetic polymorphisms in ApoE and BDNF; the effect on recovery after repeated mild traumatic brain injury and personalized treatment approaches in a mouse model

Authors: *A. O. GIARRATANA[1], L. FISH[2], R. SCHLOSS[3], S. THAKKER-VARIA[4], M. YARMUSH[3], J. ALDER[5]
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Abstract: Traumatic Brain Injury (TBI) is a serious and potentially life threatening clinical problem. Clinicians have long noticed that certain patients recover better after TBI, and identifying what makes some patients more susceptible is a vital step in understanding the underlying mechanisms through which TBI causes its deleterious effects. The goal of this study was to determine the effect of specific single nucleotide polymorphisms (SNPs), which may lend insight into whether individuals with these genetic alleles might be at higher risk than the general population for poor recovery following TBI and to explore approaches to treating them. We have investigated behavioral and cellular outcomes in genetically engineered mice with the ApoE4 and BDNF Val66Val polymorphisms following repeated, mild TBI (rmTBI) in a lateral fluid percussion model. We have found that ApoE4 and Val66Met mice trend towards having a larger injury volume as assessed by MRI and increased levels of neurodegeneration, apoptosis, gliosis, phospho-tau, and microglia compared to ApoE3 and Val66Val mice at 21 days post injury. We have seen that while injured mice have worse motor performance on the rotarod at 1, 7, and 21 days post injury, there does not appear to be a difference between the genotypes. We have begun investigating learning and memory differences between genotypes after rmTBI by using the novel object recognition test and the fluid filled Y maze. We are also exploring a personalized approach to treating genetically susceptible individuals by targeting the pathway altered in those genotypes. Human mesenchymal stromal cells have been shown to secrete neurotrophins such as BDNF. We have utilized different approaches such as encapsulation and pre-treatment of the mesenchymal cells with different factors in order to increase their therapeutic efficacy. We have found that encapsulation and pretreatment of the MSCs with factors such as forskolin may help skew their secretome towards a more positive one. This study lays the groundwork for further

investigation into the genetics that play a role in recovery after TBI and potential personalized therapeutics.

Disclosures: A.O. Giarratana: None. **L. Fish:** None. **R. Schloss:** None. **S. Thakker-Varia:** None. **M. Yarmush:** None. **J. Alder:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.04/AA35

Topic: C.09. Brain Injury and Trauma

Support: MPI funding

Title: A rat model of coma pathogenesis and recovery

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Abstract: Millions of patients worldwide experience a coma every year due to trauma, stroke, and other severe brain injuries, but the mechanisms by which patients emerge from coma are incompletely understood. A major reason for this gap in knowledge is the absence of an animal model of coma, which would provide a means to study both the pathogenesis of coma and the mechanisms that enable reemergence of consciousness. Here, we develop a rat coma model to systematically study the progression of rat brain function and behavior after coma. Endothelin-1 (ET-1), a potent vasoconstrictor, was injected into the caudal brainstem to cause hypoxic-ischemic injury to brainstem nuclei that mediate arousal, as confirmed by T2-weighted MRI. Based on the human Glasgow Coma Scale and Full Outline of UnResponsiveness, a Tübingen-Boston Rat Coma Scale was developed to quantify the severity of neurological impairment and track behavioral recovery. Cortical function was simultaneously assessed using Local Field Potential (LFP) recordings and resting-state functional MRI (rs-fMRI) connectivity mapping. Animals that recovered spontaneous breathing and brainstem reflexes showed increasing global cortical activity on LFP (**Fig.1**) and increasing whole brain functional connectivity on rs-fMRI. This is, to our knowledge, the first report of a rat coma model that enables multimodality studies of the mechanisms underlying coma pathogenesis and recovery following brainstem injury. Ongoing studies using optogenetics and calcium imaging will investigate the role of specific brainstem-thalamo-cortical circuits in the comatose brain, which will help elucidate the mechanisms that underlie coma emergence.

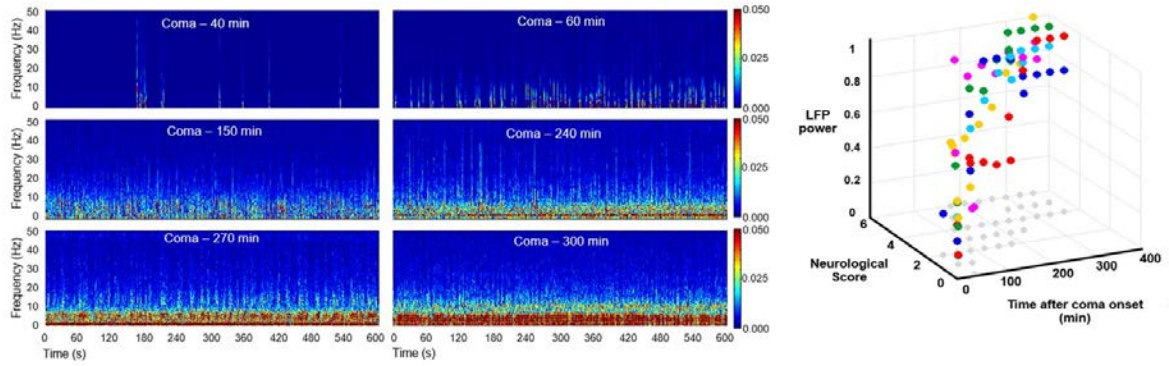

Figure 1. *A*: **Power spectrum of Local Field Potential (LFP) recorded at different times after ET-1 injection (comatose rat without anesthesia).** The isoelectric line evolves to a burst-suppression pattern and, eventually, to continuous background activity. *B*: **Temporal progression of LFP power and Tübingen-Boston Rat Coma Scale score after coma induction.**

Disclosures: P. Pais: None. **B. Edlow:** None. **Y. Jiang:** None. **M. Zou:** None. **X. Yu:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

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Program#/Poster#: 140.05/AA36

Topic: C.09. Brain Injury and Trauma

Support: DoD CDMRP W81XWH-10-1-0742

Title: Assessment of corona radiata following injury to primary motor cortex (M1) in a translational model of traumatic brain injury

Authors: H. ZHANG[1], *S. BARBAY[1], S. B. FROST[1], D. J. GUGGENMOS[1], H. M. HUDSON[1], D. T. BUNDY[1], J. C. PETERSON[2], S. L. DEJONG[4], R. J. NUDO[1,3]
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Abstract: Integrity of the corticospinal tract (CST) after cortical injury has been used as an indication of potential recovery and responsiveness to therapeutic intervention. Fibers originating from neurons in M1 and contributing to the CST mediate hand function for grip strength and dexterity. Previously we presented a squirrel monkey model of traumatic brain injury (TBI) using a controlled cortical impact (CCI) procedure (Barbay et al. (2016; PMRJ Sep 8(9S)S227). A focal impact delivered to the M1 hand area resulted in a transient impairment of handgrip strength and a persistent impairment in dexterity during three months of post-injury assessment. In the present study, we estimated the impact of the CCI to the underlying white matter in the corona radiata in three squirrel monkeys. Following the end of the behavioral assessment period a digital photograph of the cortex was obtained, and using surface vasculature for reference,

compared with a pre-injury photograph to assess loss of the M1 hand area. The extent of the injury was confirmed in post-mortem coronal sections (40µm) through M1 that were stained for myelin (Weil Silver stain; Neuroscience Assoc.). The reduction of fibers passing through the corona radiata was assessed quantitatively by measuring white matter volume in both hemispheres using a Cavalieri estimator probe (Stereo Investigator; Microbrightfield Inc.) through the extent of the M1 hand area. All three monkeys showed a reduction in the corona radiata ipsilateral to the injury in comparison to the intact hemisphere. The corona radiata measurements are consistent with results from other NHP studies and clinical assessments showing the differential effects that damage to the CST has upon handgrip and dexterity. Cortical lesion size is often difficult to assess accurately after tissue necrosis has occurred weeks to months after injury. This is particularly problematic in large animal models with focal lesions where the necrotic grey matter is a small percentage of the total cortical volume. We propose that morphometric analysis of the corona radiata may provide a more accurate measure of lesion volume, and presumably, a better predictor of motor impairment.

Disclosures: H. Zhang: None. **S. Barbay:** None. **S.B. Frost:** None. **D.J. Guggenmos:** None. **H.M. Hudson:** None. **D.T. Bundy:** None. **J.C. Peterson:** None. **S.L. DeJong:** None. **R.J. Nudo:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.06/BB1

Topic: C.09. Brain Injury and Trauma

Support: NINDS: 1R01NS101108-01

Title: Laminar and single unit recordings of the hippocampus in behaving rodents after traumatic brain injury reveal field and neuronal coding disruptions

Authors: *R. J. RUSSO[1], P. F. KOCH[1], C. D. ADAM[1,2], M. T. WEBER[1], V. E. JOHNSON[1], J. A. WOLF[1,2]
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Abstract: Persistent memory deficits are a major sequela of TBI, yet network level mechanisms of memory impairment are poorly understood. Studies using the fluid percussion injury model (FPI) have reported decreased theta power in the hippocampus (HC), but how this reduction influences memory-relevant HC networks and coding of memory remains unknown. We have previously examined HC circuitry acutely in this model of TBI, demonstrating robust changes in

field architecture as well as changes in CA1 neuronal entrainment to HC theta. Limitations of these electrophysiological recordings under anesthesia motivated recordings from chronically implanted HC electrodes in the awake, freely moving rodent to facilitate examination of hippocampal networks engaged in relevant behavior after injury. We demonstrate robust extracellular field potentials and stable unit recordings post-implant following FPI out to 14 days post-injury. Experimental TBI was induced in male Sprague Dawley rats by FPI at mild to moderate (1.6-1.8 atm) severity. Implantation of multi-shank silicon probes with 32-64 electrodes on a high-resolution microdrive allowed for recordings of single units and simultaneous laminar field potentials. These recordings were also acquired while animals freely traversed an open field and a radial arm maze using 64-channel wireless telemetry. Preliminary results from acute and chronic recordings indicate that distribution of preferred phase in injured CA1 neurons exhibited two sharp peaks in contrast to a wide distribution with a single peak in non-injured animals. However, CA1 neurons do remain entrained to theta in non-injured and injured animals. These results point to abnormal theta entrainment which could cause failure to coordinate neuronal ensembles that represent place during memory tasks. Distribution of axonal injury (revealed with amyloid precursor protein) suggest that loss of inputs from entorhinal cortex and medial septum may contribute to these changes in addition to reduction in performance on the Morris Water maze. Ongoing work to characterize memory deficits in the radial arm maze combined with awake recordings during this memory task will elucidate mechanisms of trauma-induced network dysfunction.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.07/BB2

Topic: C.09. Brain Injury and Trauma

Support: CURE

VA Office of Research and Development

Title: 2DG following brain injury reduces late posttraumatic epilepsy in a unique model of TBI with frequent generalized posttraumatic seizures in “fast” kindling-susceptible PPKS rats

Authors: *P. A. RUTECKI[1,2], R. KOTLSOKI[1,2], M. HANSON[1], T. SUTULA[1]
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Abstract: Human post-traumatic epilepsy (PTE) typically develops with delayed onset during the first year after TBI and ~ 12.6% of new unprovoked seizures present as late as 14 years after injury. The delayed onset of seizures after TBI supports the view that PTE is a slowly developing process of epileptogenesis during evolving neural circuit alterations and plasticity after initial injury, potentially sharing common mechanisms with other slowly evolving processes of circuit plasticity such as lesion-induced plasticity and seizure-induced kindling. The slow development of PTE provides an attractive temporal window for antiepileptogenic intervention to prevent PTE, but multiple large human clinical trials with anticonvulsants following injury have not reduced PTE and experimental studies in rodent models have been limited by relatively infrequent spontaneous seizures. To address these clinical and experimental gaps, we evaluated the effects of 2-deoxy-D-glucose (2DG), a reversible glycolytic inhibitor with novel acute anticonvulsant and chronic antiepileptic "disease-modifying" actions on emergence of PTE in "fast" perforant path kindling-susceptible (PPKS) rats with genetic background conferring susceptibility to seizure-induced circuit plasticity (Langberg et al., Neurobiol Dis 85:122-129, 2015). In this model, video-EEG from 1-6 months after controlled cortical impact (CCI) demonstrated frequent focal and generalized spike-wave seizures (GSWS) occurring as often as every 1-5 minutes with durations of ~8-15 sec and behavioral accompaniment of "freezing" in 16 of 32 PPKS rats. The duration and frequency of the seizures increase during 1-6 months of recording after injury. 2DG (250 mg/kg/day) for 2 weeks, a dose which reduces kindling progression in outbred Sprague Dawley rats by 2-fold (Stafstrom et al., Ann Neurol, 2009), significantly reduced the occurrence of GSWSs after CCI (3 of 15 rats, $p<0.033$, chi-square). The effect of 2DG was dose-dependent as 8 of 15 PPKS rats treated with 50 mg/kg/day demonstrated frequent GSWSs as observed in saline-treated controls. The results confirm that CCI in kindling-susceptible PPKS rats is a practical model for PTE with frequent seizures, and demonstrate the brief 2DG treatment after initial injury has potential to reduce development of PTE.

Disclosures: P.A. Rutecki: None. **R. Kotlsoki:** None. **M. Hanson:** None. **T. Sutula:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurogenomex, Inc.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.08/BB3

Topic: C.09. Brain Injury and Trauma

Title: Behavioral and protein changes in an adult zebrafish mTBI model

Authors: *R. SPENCE[1], V. GILL[1], A. IBRAHIM[1], J. SUN[2], A. BOOKER[2], H. THOMASON[2]
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Abstract: We have recently developed an adult zebrafish model of mTBI using a non-puncturing weight drop method. Previous data from our model quantified transcriptomic and proteomic changes that occur pre-injury, during injury and post-injury when the brain is undergoing neuroregeneration. Currently our focus is two-fold. First, to test a behavioral paradigm to explore the effect of mTBI on learning and memory. Our hypothesis is that mRNA and proteomic changes could be indicative of behavioral deficits in learning and memory. Second, we wish to determine the anatomical locations of inflammation and cell proliferation in our mTBI model. We hypothesize that inflammation and cell proliferation might be occurring in overlapping regions, and thus mechanistically related. Our work will try and determine how changes at the mRNA and protein level relate to behavior in mTBI.

Disclosures: R. Spence: None. **V. Gill:** None. **A. Ibrahim:** None. **J. Sun:** None. **A. Booker:** None. **H. Thomason:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.09/BB4

Topic: C.09. Brain Injury and Trauma

Title: Paternal epigenetic legacy - mechanisms influencing susceptibility to post-concussion symptomology

Authors: *H. HEHAR[1], I. MA[2], R. M. MYCHASIUK[3]
[1]Room 274, [3]Neurosci., [2]Univ. of Calgary, Calgary, AB, Canada

Abstract: There are widespread differences in individuals' responses to equivalent brain injuries, which are likely a result of pre-existing differences in brain plasticity and organization. Although previous studies have demonstrated a link between paternal experiences, such as High fat diet (HFD) and Advanced Age (AA), and offspring Post Concussive Syndrome susceptibility, the mechanisms that mediate the link between paternal experiences and brain injury outcomes remain unknown. In an effort to understand these mechanisms, this study investigated whether paternal experiences prior to conception stably modify epigenetic tags, specifically DNA methylation, thus permitting transmission of gene expression states to their sons. Additionally, since telomere length is associated with neurological health, this study also examined whether this paternally inherited trait was altered based on paternal experiences. Sprague-Dawley fathers were randomly assigned to HFD, AA, or Control treatment groups, mated, and tissue from the paternal sperm as well as brain and sperm of offspring was analyzed. Using the MethyLight technique, promoter methylation of specific genes involved in recovery from concussion and brain plasticity (*Bdnf, Lept-R, Oxy-R,* and *Tert*) was analyzed. Paternal experiences altered sperm promoter methylation in fathers. In many cases, promoter methylation was similar in paternal

sperm and respective sons' sperm and brain, demonstrating transmission of stable epigenetic tags. Additionally, for certain genes, sperm gene methylation was altered following a concussion, suggesting that concussions can alter the paternal epigenome and thus influence future offspring traits. qRT-PCR technique also demonstrated that telomere length was consistent across fathers and their sons, and between brain and sperm. Older fathers were an exception to this finding, as they exhibited increased sperm telomere length, which was not evident in sperm or brain of their sons. Paternal experiences thus have transgenerational effects on offspring sperm and brain DNA methylation and telomere length, which likely play a role in explaining differences in outcomes post concussion. This study provides further evidence for the need to investigate the role played by peoples' epigenome in concussion prognosis and target treatment accordingly.

Disclosures: H. Hehar: None. **I. Ma:** None. **R.M. Mychasiuk:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.10/BB5

Topic: C.09. Brain Injury and Trauma

Title: Advanced MR imaging of repetitive TBI in adolescent male rats

Authors: *J. CHRISTENSEN[1], G. R. YAMAKAWA[2], D. WRIGHT[4], S. R. SHULTZ[5], R. M. MYCHASIUK[3]
[2]Psychology, [3]Neurosci., [1]Univ. of Calgary, Calgary, AB, Canada; [4]Florey Inst., Melbourne Univ., Melbourne, Australia; [5]Med., Univ. of Melbourne, Parkville, Australia

Abstract: Traumatic Brain Injury (TBI) is one of the most common, yet neglected, pediatric health issues in North America. Specifically, individuals who experience repetitive mild TBI (RmTBI) generally exhibit poorer developmental outcomes. Some possible causes for the poor neurological outcomes associated with RmTBI include alterations in functional networks, neuroanatomical modifications, or deficient removal of injury-induced waste. The glymphatic system is a brain-wide paravascular pathway that is responsible for the clearance of macroscopic waste from the central nervous system. This waste removal system appears to be more active during periods of sleep as it is radically inhibited during wakefulness. Since sleep disturbances are regularly reported after experiencing a TBI, the glymphatic system seems to be a promising candidate in explaining the development of post-concussive syndrome. Therefore, we induced three mild traumatic brain injuries (mTBI) in adolescent male rats prior to volumetric and diffusion magnetic resonance imaging (MRI). MRI scanning was employed to evaluate structural changes in the corpus callosum and the prefrontal cortex. During the MRI procedure, an injection of gadolinium, a paramagnetic contrast agent, was situated within the cisterna magna to allow for visualization and assessment of glymphatic system function. A behavioural test battery, which

included beamwalk, openfield, elevated plus maze, novel context mismatch, and force swim, was utilized to assess symptomology consistent with post-concussive syndrome. RmTBI produced behavioural impairments that mimic post-concussive syndrome in patient populations and resulted in diffusion MRI changes in the corpus callosum of the male adolescent rats, which is a marker of axonal injury. Glymphatic system assessment MRI scanning is currently underway with results to follow.

Disclosures: J. Christensen: None. **G.R. Yamakawa:** None. **D. Wright:** None. **S.R. Shultz:** None. **R.M. Mychasiuk:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.11/BB6

Topic: C.09. Brain Injury and Trauma

Support: Developmental Neurosciences Research Startup Costs

Title: Circadian rhythms in adolescent rats sustaining repetitive mild traumatic brain injuries

Authors: *G. R. YAMAKAWA[1], R. M. MYCHASIUK[2]
[1]Psychology, [2]Neurosci., Univ. of Calgary, Calgary, AB, Canada

Abstract: Mild traumatic brain injury (TBI) is one of the most expensive pediatric health problems in North America. Adolescents are at particularly high risk for mild TBI and most specifically, repetitive mTBI (RmTBI) due to life long involvement in sports. 15-20% of adolescents with RmTBI go on to suffer from post-concussive symptomologies that persist for months to decades. Even more problematic, RmTBI has been linked to early onset cognitive decline and neurodegenerative disorders such as Alzheimer's and dementia. Little is known about the factors that increase the risk of concussion, the factors that influence behavioral outcome, or what can be done to aid in the recovery. Given that 70% of individuals report sleep problems, including insomnia, and research has established a significant relationship between sleep disturbances and neurodegeneration, it is imperative that we understand the relationship between sleep and RmTBI in this vulnerable population. To begin to examine this, we implanted telemetry probes into the intraperitoneal cavities of male and female Sprague Dawley rats. Throughout the experiments, general locomotor activity and body temperature rhythm data transmitted by the probes were continuously collected. We next subjected the rats to RmTBI using our lateral impact device. In experiment 1 we subjected adolescent male and female rats to RmTBI 3 days apart in 12:12 hr light/dark cycles before placing them and constant dark for 4 days. In experiment 2, we placed adolescent females in constant dark following each TBI to observe the output of the endogenous circadian pacemaker in absence of environmental cues. At

the conclusion of the experiments, the rats were perfused and brains collected to be processed for immunohistochemical markers of damage. We found that adolescent females in experiment 1 showed hyperactivity in constant dark. The circadian rhythms of locomotor activity and body temperature rhythms remained highly resilient to RmTBI otherwise. These results suggest that in some cases, the underlying output of the master circadian pacemaker may be disrupted by RmTBI, there may be sex differences and these differences do not become apparent until rats are in placed in constant dark.

Disclosures: G.R. Yamakawa: None. **R.M. Mychasiuk:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.12/BB7

Topic: C.09. Brain Injury and Trauma

Title: Diffusion tensor imaging detects acute and chronic changes due to traumatic brain injury in a blast injured rat model

Authors: *P. N. VENKATASUBRAMANIAN[1], L. LI[1], D. AKSENOV[1], P. KENI[2], S. A. SHERMAN[2], B. SINDELAR[2], J. FINAN[2], J. E. BAILES, Jr[2], A. M. WYRWICZ[1]
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Abstract: Introduction
Traumatic Brain Injury (TBI) is a leading cause of mortality and morbidity but remains difficult to diagnose due to lack of specificity and sensitivity in common imaging techniques. Diffusion tensor imaging (DTI) enables measurement of the diffusion of water in tissue and has been successful in studying white matter tracts in vivo, the most common location for pathology in TBI. The purpose of this study is to characterize the temporal evolution of TBI due to blast injury in a rat model. Using DTI we have detected acute and chronic changes in the corpus callosum (CC) that suggest axonal damage.
Methods
Blast injury was administered to Sprague-Dawley rats to the right side of the head at an average pressure of 58.6 psi via blast tube. These blast-injury rats, along with a control group that did not undergo any injury, were imaged in vivo using EPI-DTI one day (D1) and 14 days (D14) post injury (n=5). Diffusion images were analyzed to calculate four metrics of DTI for each pixel: fractional anisotropy (FA), trace, and axial and radial diffusivity. DTI parameters were measured in six regions of interest: the medial right and left CC, the lateral right and left CC and the right and left cingulum. Furthermore, these regions were analyzed in six coronal slices of the brain comprising the splenium, body and genu of the CC. Regions of interest were manually drawn onto each image using visual anatomical landmarks to better accommodate the variations in

anatomy between each rat. The blast injury rats were compared to the control group at the two timepoints for all four DTI parameters using standard one-tailed, unequal variance t-tests.

Results

At D1, injured rats showed lower FA, higher trace, and higher axial and radial diffusivity in many regions of the CC and cingulum when compared to the control group. Notably, in the medial CC there was a 7.4% decrease in FA ipsilateral to blast injury, but only a 1.8% decrease contralaterally. At D14, the injured rats showed higher FA and lower trace in all regions of the CC and cingulum, with no significant differences between the left and right sides. Furthermore, injured rats showed higher radial diffusivity and lower axial diffusivity in the CC, and lower radial and axial diffusivity in the cingulum. The decreased FA in TBI rats at D1 indicates demyelination and disruption of white matter structure due to axonal injury from the blast. The subsequent increase in FA at D14 shows evidence of white matter tract recovery through excessive remyelination.

Conclusion

The results from this study support the potential of DTI to differentiate brain changes associated with acute and chronic phases of blast injury.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.13/BB8

Topic: C.09. Brain Injury and Trauma

Support: ISDH Grant No. 204200

NIH Grant NS073636

NIH R21 NS090244-01

NIH R01 862 DC011580

Indiana CTSI CBR/CTR Grant RR025761

Title: Neural responses to sounds in noise and speech-like sounds following blast exposure

Authors: *E. X. HAN[1], J. LAI[2], N. RACE[3], R. SHI[4], E. L. BARTLETT[1]
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Abstract: Blast exposure during explosive events is one of the main causes of acute hearing deficit. Since head blast induces blood-brain barrier damage and inflammatory responses in the caudoventral portion of the brain where olivary and lemniscal afferents to inferior colliculus (IC) are located, these regions and the IC may be substantially altered by blast. Previous research of our group has confirmed significant and persistent (2 weeks and one month) but relatively small impacts on auditory evoked potentials (AEP) of rats exposed to mild blast using brief clicks and tones along with 100% sinusoidally amplitude modulated (AM) stimuli. The current study compares the impact of noise exposure and blast exposure on processing auditory stimuli more complex and relevant to speech, including AM stimuli in challenging contexts (noise and reduced depth), as well as speech-like stimuli, using non-invasive AEP. Over multiple time points up to 2 months post blast, EFR responses are greatly diminished for slow AM in blasted animals, both in 100% conditions and in noise or reduced depth. The results of our research suggest diagnostic avenues and brain regions to inspect further for neurodegeneration and physiological changes at the neuronal level.

Disclosures: E.X. Han: None. **J. Lai:** None. **N. Race:** None. **R. Shi:** Other; Riyi Shi is a co-founder of Neuro Vigor, a company developing novel drug treatments and diagnostic approaches for neurodegenerative diseases and neurotrauma.. **E.L. Bartlett:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.14/BB9

Topic: C.09. Brain Injury and Trauma

Support: NINDS Grant R01 NS081068

Title: Repeat mild TBI causes functional changes in the absence of synapse loss, neuron cell death and neuroinflammation

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Abstract: Mild traumatic brain injury (mTBI) is defined as a trauma-induced alteration in brain function in the absence of structural damage. Recently we described an experimental model of mTBI that resulted in a temporary loss of synapses following a single mTBI. In this study, we examined how 30 mTBI delivered over 6 days (5 mTBI per day) affected outcomes in C57Bl/6 mice. Mice were exposed to either daily isoflurane (3 minutes per day for 6 days) or daily isoflurane followed by 5 rapid succession mTBI for 6 consecutive days (30 mTBI total). Immunohistochemical analyses revealed that 30 mTBI over 6 days did not cause grey matter

inflammation, neuronal or glial cell death, or axonal injury. Golgi staining for dendritic spines indicated that there was no change in the number of excitatory synapses in repeat mTBI mice compared to the sham mice. In separate cohorts, we performed behavioral testing and electrophysiology. Morris Water Maze testing revealed that there were deficits in both the acquisition and probe trial phases, indicating impaired learning and memory. Elevated Plus Maze test revealed that repeat mTBI mice had enhanced risk-taking behavior. EEG for sleep cycle and brain wave analysis revealed chronic disruptions in awake oscillations and sleep cycles of repeat mTBI mice. Extracellular field recordings in the hippocampus in acute slice preparations revealed that repeat mTBI mice showed impaired long-term potentiation (LTP). Taken together, our findings suggest that repetitive mTBI (30 mTBI over 6 days) causes impaired learning, memory, and overall brain function in the absence of structural damage or a decrease in the number of excitatory synapses. We hypothesize that synaptic adaptation occurs after repeat mTBI in order to protect neurons from repeated exposure to excitotoxicity, but at the cost of normal function. Future experiments will use electrophysiology to determine how neurons adapt at the synaptic level to repeat mTBI.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.15/BB10

Topic: C.09. Brain Injury and Trauma

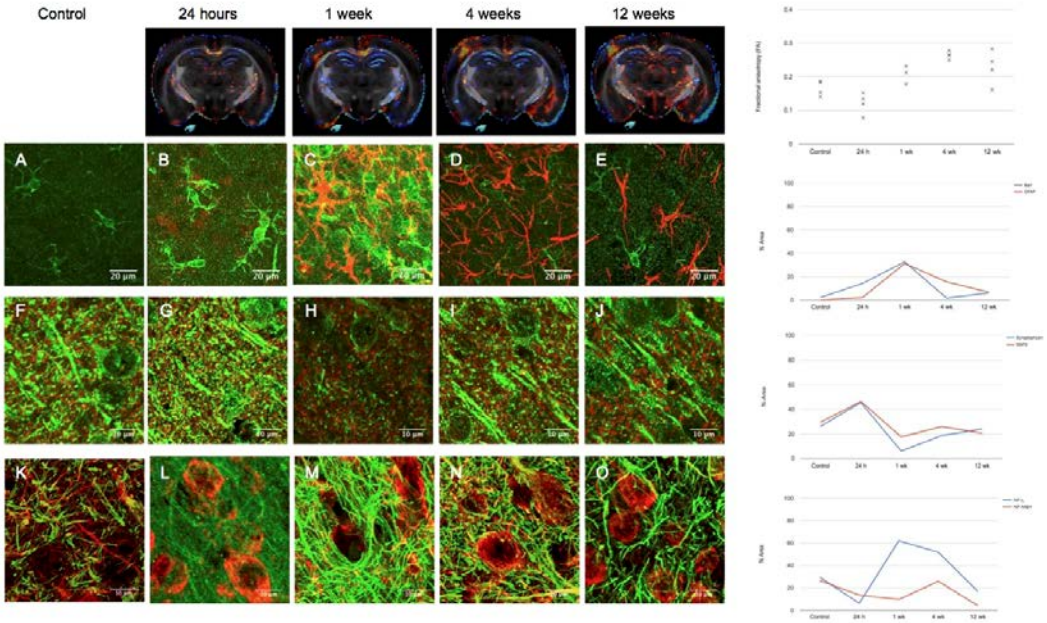
Support: CNRM

Title: Contributions of glia, neuron, and synapse density to abnormal DTI metrics following mild TBI

Authors: *S. G. KING[1,3], E. B. HUTCHINSON[4,2], S. C. SCHWERIN[5], M. HABER[6], S. L. JULIANO[7]
[1]Henry Jackson Fndn., Washington, DC; [2]Henry Jackson Fndn., Bethesda, MD; [3]Qmi/nibib, [4]QMI/NIBIB, NIH, Bethesda, MD; [5]Anatomy, Physiol. and Genet., Uniformed Services Univ., Bethesda, MD; [6]Neurol., Univ. of Pennsylvania, Philadelphia, PA; [7]USUHS, Bethesda, MD

Abstract: Diffusion tensor imaging (DTI) is sensitive to tissue abnormalities after mild traumatic brain injury (mTBI). However, relationships between DTI abnormalities and cellular alterations such as gliosis and neural degeneration [1, 2], are poorly understood. Previously, increased cortical fractional anisotropy (FA) was observed in a chronic period after mild controlled cortical impact (mCCI) in mice [3]. We conducted immunohistochemical staining in

these same samples to identify contributions of tissue characteristics to FA abnormalities.
Adult male mouse brains were obtained 24 hours, 1 week, 4, and 12 weeks after mCCI in the somatosensory cortex. Markers for astrocytes (GFAP), microglia (Iba1), soma & dendrites (MAP2), synaptic vesicles (synaptophysin), and neurofilament (NF) subunits were visualized in the perilesion & contralateral cortex on a Zeiss 710 confocal. Quantitative analysis was performed in ImageJ using the “percent area” approach with manually standardized threshold to measure stain density and orientation analysis was applied for local coherency values.
Results are displayed in the figure. In the injured cortex, FA increased at 4 and 12 weeks post-mCCI, but not earlier. Iba1 and GFAP (green & red, A-E) showed gliosis in deep layers of the injured cortex, peaking 1 week post-mCCI, consistent with known glial changes post-trauma. Synaptophysin (red, F-J) density was highest at 24 hours, and lowest at 1 week with regrowth at 4 weeks. NF medium- and heavy-positive axons (red, K-O) decreased, with marked increase in NF light-positive axons (green, K-O) at 1 and 4 weeks.
In addition to confirming gliosis with altered FA in the cortex post-CCI, our results show changes in synapse and dendrite density and increased density of small caliber axons after mCCI. These findings are consistent with a potential role for regrowth and plasticity in regions of abnormal DTI metrics following mTBI.
[1] M.D. Budde et al., Brain : A Journal of Neurology, (2011).[2] J. Zhuo et al., NeuroImage, 59 (2012) 467-477.[3] E. Hutchinson et al., NCA TBI Research Symposium, March 2015, Bethesda, MD



Disclosures: **S.G. King:** None. **E.B. Hutchinson:** None. **S.C. Schwerin:** None. **M. Haber:** None. **S.L. Juliano:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.16/BB11

Topic: C.09. Brain Injury and Trauma

Support: NJCBIR-CBIR15IRG014

Title: Changes in blood pressure, heart rate and baroreflex after severe, moderate and mild fluid percussion injury in Wistar rats

Authors: *V. C. CHITRAVANSHI[1], Y. UMEMOTO[2], H. N. SAPRU[3]
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Abstract: ABSTRACT
In the present studies, fluid percussion injury (FPI) was used to produce traumatic brain injury (TBI) in Wistar rats weighing 325-350 gm, anesthetized with isoflurane and urethane. FPI causes primary injury by external physical force which leads to secondary injury by biological processes such as metabolic, cellular, and other molecular actions that ultimately results in brain cell death, tissue and nerve damage and atrophy causing disabilities and high death rates. In this study, acute and chronic effects after the severe (2.8-3.6 atmospheres), moderate (1.5-2.2 atmospheres) and mild (0.1-1 atmospheres) FPI was investigated on systemic blood pressure (BP) and heart rate (HR). Furthermore, changes in baroreflex after the moderate and mild FPI were also studied along with changes in greater splanchnic nerve activity (GSNA). Application of severe, moderate and mild Fluid percussion injury (FPI) resulted in 100%, 40% and 10% mortality, respectively. The rats were unconscious for 7.1 ± 1.6 min and 5.3 ± 0.9 min after application of moderate and mild FPI, respectively. Application of moderate and mild FPI resulted in apnea for 38.2 ± 17.3 and 14.8 ± 3.6, respectively. The decreases in MAP elicited by application of moderate FPI were 16.8± 3.1%, 18.7 ± 2.6%, 43.1 ± 2.1%, 61 ± 2.8% and 63.2 ± 3% (mmHg) after 30, 1, 2, 4 and 6 hrs of injury, respectively. The decreases in HR elicited by moderate FPI were 7.8± 1.7%, 11.3 ± 2.9%, 14.2 ± 4.1%, 15.7 ± 4.3% and 18.5 ± 4.4% (bpm), respectively, at the same time points. The decreases in mean arterial pressure (MAP) elicited by mild FPI after 30, 1, 2, 4 and 6 hrs of injury were 14.5 ± 3.3%, 17.7 ± 2.5%, 37.4 ± 4.3%, 59.1 ± 3.1% and 61.9 ± 2.4% (mmHg). The decreases in HR elicited by mild FPI at same corresponding time points were 5.5 ± 2.1%, 9.1 ± 2.8%, 10.6 ± 4.1%, 12.4 ± 4% and 15.6 ± 3.9% (bpm), respectively. These results indicate that both moderate and mild FPI elicit decreases in MAP and HR along with a decrease in the greater splanchnic nerve activity (GSNA) which was also reduced after the moderate and mild FPI. In mild FPI the decreases in MAP and HR of acute FPI treated rats were significantly different from sham. There were significant decreases in MAP of acute FPI (moderate) when compared with

the decreases in MAP of 3 day and 7 day after the FPI rats, however, only significant differences were in HR of rats at 30 minutes after the FPI (moderate). The baroreflex sensitivity was also attenuated after the moderate and mild FPI. (*p< 0.05, **p<0.01, ***p<0.001, ****p<0.0001).
SUPPORT: NJDOH- NJCBIR15IRG014

Disclosures: V.C. Chitravanshi: None. **Y. Umemoto:** None. **H.N. Sapru:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.17/BB12

Topic: C.09. Brain Injury and Trauma

Support: University of Georgia Research Foundation

Title: Characterization of traumatic brain injury utilizing non-invasive magnetic resonance imaging and histological assessment in a piglet model

Authors: *M. N. WENDZIK[1], ***M. N. WENDZIK**[1], E. W. BAKER[2], H. A. KINDER[2], S. L. WANG[4], H. MAO[4], F. D. WEST[3]
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Abstract: Traumatic brain injury (TBI) is a major cause of death and disability in the United States, chiefly affecting children ages 0-4 years. TBI at such a young age may lead to long-term neurological deficits. Animal models not truly representative of the human condition have impeded development of a translatable TBI treatment, suggesting a more human-like animal model, such as a piglet, is necessary for developing an effective therapy. Magnetic resonance imaging (MRI) and histological assessments are pertinent in the comprehensive understanding and treatment of TBI at the tissue and cellular levels. We hypothesized that controlled cortical impact (CCI) would result in a concussive piglet TBI model with substantial changes in lesion and hemisphere volume coupled with distinct histological changes that persist over time. TBI was induced in six male piglets, with MRI scans conducted 24 hours and 12 weeks post-TBI to measure the lesion size and midline shift. Histological changes were observed by quantifying NeuN+ neurons, GFAP+ astrocytes, and Iba1+ microglia in the cortical peri-lesion area at 1 day, 1 week, 4 weeks, and 12 weeks post-TBI. Lesion size at 24 hours post-TBI was 3.44 cm3 (0.52) with a midline shift of +1.80 mm (0.46). Lesion size was significantly reduced comparatively at 12 weeks to 1.95 cm3 (0.44) with a significant change midline shift of -2.98 mm (0.29) as compared to 1 day post TBI. The observed directional change in midline shift and decrease in lesion size can be attributed to attenuated swelling and significant brain atrophy. We observed a substantial decline in NeuN+ ($p<0.01$) neurons suggesting there was significant cell death in

response to the injury that never recovered over a 12 week timecourse. We also observed a significant upregulation in GFAP+ astrocytes ($p<0.0001$) and Iba1+ microglia ($p<0.05$), which suggests that TBI leads to gliosis and inflammatory response that mounts over time in response the injury. The characterization of key cytoarchitectural changes in the CCI TBI piglet model will enable more robust and predictive assessments of novel therapeutics that will likely lead to more success in human clinical trials.

Disclosures: **M.N. Wendzik:** A. Employment/Salary (full or part-time):; University of Georgia. **E.W. Baker:** A. Employment/Salary (full or part-time):; University of Georgia. **H.A. Kinder:** A. Employment/Salary (full or part-time):; University of Georgia. **S.L. Wang:** A. Employment/Salary (full or part-time):; Emory University. **H. Mao:** A. Employment/Salary (full or part-time):; Emory University. **F.D. West:** A. Employment/Salary (full or part-time):; University of Georgia.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.18/BB13

Topic: C.09. Brain Injury and Trauma

Support: Congressionally Directed Medical Research Programs (CDMRP) AZ140109

Peer Reviewed Alzheimer's Research Program (PRARP) Convergence Science Research Award

Department of Pathology & Anatomical Sciences at the University of Missouri School of Medicine

Title: The behaviors and neuropathology linked with biophysics in a murine model of open-field blast-induced mild traumatic brain injury

Authors: *H. SONG[1], L. KONAN[1], J. CUI[1], T. A. NDAM[1], A. SIMONYI[2], C. E. JOHNSON[4], I. CERNAK[5], U. DEMIRCI[6], G. HUBLER[3], R. G. DEPALMA[7], Z. GU[1]
[1]Pathology and Anatom. sciences, [2]Biochem., [3]Dept. of Physics and Astronomy, Univ. of Missouri, Columbia, Columbia, MO; [4]Dept. of Mining and Nuclear Engin., Missouri Univ. of Sci. and Technol., Rolla, MO; [5]Canadian Military and Veterans' Clin. Rehabil., Univ. of Alberta, Edmonton, AB, Canada; [6]Dept. of Radiology, Stanford Univ. Sch. of Med., Stanford, CA; [7]Office of Res. and Develop., DVA, Washington, DC

Abstract: The majority of injuries including traumatic brain injuries (TBI) inflicted in recent military actions in Afghanistan and Iraq has been caused by explosive weaponry. Out of 361,092 TBIs reported by the Department of Defense, over 82%, many of them blast-induced, has been

classified as mild TBI (mTBI). This injury and its late effects in certain combatants has been considered as a “signature injury” in recent combat. The injury is also invisible using conventional brain CT scanning. Although mTBI is not a typically gross injury, the physics of blast detonation predict that low levels of blast energy can strike deeply into the brain causing subcellular or ultrastructural damage. Energy is deposited as the shockwave passes through brain tissue, and calculations based on phonon characteristics of brain water predict that mTBI pathology occurs at nanoscale intervals ranging from ~5 to 200 nm to cause rupture of cellular components and membranes. Experimental blast models have provided insights of brain injury; however, the underlying mechanisms of how blast wave exposure induces cognitive and behavioral impairments remain controversial. Using a model of open-field blast-induced mTBI in C57BL/6J mice, we first established an experimental blast setting using the high-energy explosive C4 at 350 grams in an ambient condition, without any interference. In prone position facing towards the explosive, anesthetized animals were placed on an unobtrusive platform allowing free passage of the shock front placed 1 meter above ground. Blast waves and peak overpressures were recorded by pencil pressure gauges and high speed cameras from various angles up to 16,000 frames per second. We observed significant deficits in neurological assessment at 1, 3, and 7 days post injury (DPI). Moreover, we found impaired nest building ability, reduced exploratory/locomotor activity and higher anxiety levels in the blast exposed animals, as compared to sham controls. Silver staining in exposed mice revealed diffuse axonal injury at 7 DPI in the regions of cortex and white matter including corpus callosum & external capsule. Transmission electron microscopy showed myelin sheath deficits and mitochondrial degeneration. In summary, we have identified behavioral/neurological consequences and ultrastructural abnormalities of blast-induced mTBI in a murine model. This model permits detailed analysis of blast physics effects on brain tissue. It also provides a useful platform to elucidate linkages between blast exposure, neural functionality and underlying ultrastructural neuropathology as well as for assessing potential treatment strategies.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

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Program#/Poster#: 140.19/BB14

Topic: C.09. Brain Injury and Trauma

Support: W81XWH-15-2-0024

W81XWH-16-2-0002

Title: Effects of blast shockwave exposure on ears and auditory signal processing centers in rodents

Authors: *Y. WANG[1], R. URIOSTE[1], Y. WEI[1], Y. SU[1], K. HOLLINGSWORTH[2], W. DRIWECH[1], D. WILDER[1], V. SAJJA[1], P. ARUN[1], T. FITZGERALD[2], M. WISE[1], S. VAN ALBERT[1], W. CHANG[2], I. GIST[1], M. KELLEY[2], J. LONG[1]
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Abstract: Auditory deficits are particularly prevalent in blast victims. To better understand the mechanisms underlying blast related auditory injuries, we longitudinally studied auditory brainstem responses (ABR) to blast overpressure (BOP) exposure and assessed the associated damage to the ear and brain. Isoflurane anesthetized mice (CBA, male, 25 g) and rats (SD, male, 350 g) were secured in an Advanced Blast Simulator (ABS) in a prone position facing the oncoming shockwave. BOP (peak static pressure of 4, 8, 12 and 19 psi and 4 msec positive phase duration) was generated by Valmex membrane ruptures in the ABS. Noise controls were anesthetized and placed immediately outside the ABS and exposed to the noise but not the shockwave associated with membrane rupture. Sham controls were handled similarly without exposure to either the noise or shockwave. DPOAE signals were undetectable immediately after BOP exposure and their disappearance persisted over months, suggesting significant damage to the inner ear. ABR thresholds and latencies increased and amplitudes decreased in BOP-exposed animals relative to preinjury baselines and recordings in the sham and noise controls. These changes were observed over the entire acoustic frequency spectrum and persisted over months. Low frequency (8 kHz) hearing recovered more readily than high frequency (40 kHz) hearing. BOP damage to the tympanic membrane, middle and inner ear structures, as well as brainstem and auditory cortex were observed. Blast intensity-dependent damage to middle and inner ears was evident with no significant differences between left and right ears. Tympanic membranes were ruptured immediately following BOP exposure and resolved within a month. Labyrinthine hemorrhage was prominent from 1 day up to 14 days post-injury. Morphological evaluation of the inner ear showed hair cell loss and decreased neurons in spiral ganglia at 28 days post-injury when compared to the sham control. Brain pathology showed acute changes of dendritic spines in the auditory cortex along with neuronal degeneration and glial cell proliferation in the brainstem. Thus, BOP-induced hearing loss can be associated with disruptions to ear structures and damage to brain regions associated with the sound processing. The model of ABS-induced auditory deficits in rodents can be used for studying the mechanisms of hearing impairment after blast exposure and for evaluating potential strategies for prevention and cure.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

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Program#/Poster#: 140.20/BB15

Topic: C.09. Brain Injury and Trauma

Support: NIH 2R42AG044024-01

Title: Novel model of accelerated cognitive deficits incorporating oxidative stress and traumatic brain injury with exacerbated neuropathology

Authors: *S. H. LEE, M. BEN AISSA, Y.-T. WANG, E. NEPOMUCENO, D. GONZALEZ, G. R. J. THATCHER
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Abstract: Oxidative stress (OS) markers are seen at early stages of dementia and has been hypothesized to be a contributing factor to the secondary cascade in traumatic brain injury (TBI). OS has broader implications as a contributor to accelerated cognitive impairment, neuroinflammation, and neurodegeneration. Increased OS related to dementia and brain injury leads to an accumulation of lipid peroxidation products (LPx), notably 4-hydroxynonenal (4-HNE). 4-HNE forms protein adducts that can act as toxic secondary messengers resulting in the dysregulation of signaling pathways involved in mitochondrial and neuronal function. In addition, 4-HNE have been shown to increase following TBI and have been suspected to accelerate and exacerbate the damage in the secondary cascade of TBI. However, the exact involvement and contributing role of 4-HNE in both accelerated cognitive deficits and neuroinflammation in TBI are yet to be elucidated. By utilizing a knock-out of an enzyme responsible for detoxifying 4-HNE, aldehyde dehydrogenase (*Aldh2*$^{-/-}$) mice and weight drop closed head injury model in the *Aldh2*$^{-/-}$ mice, our goal was to characterize the contribution of LPx/4-HNE to accelerated cognitive deficits and the biochemical and functional damage of TBI. In the *Aldh2*$^{-/-}$ mice where the OS represented a "1st hit", our studies revealed that the *Aldh2*$^{-/-}$ mice exhibited increased levels of 4-HNE and demonstrated accelerated cognitive deficits. Therefore, we utilized a chemoproteomic approach to identify a network of proteins linked to accelerated dementia and to characterize an oxidative stress model mediated by LPx. Proteins differentially expressed contributed to mitochondrial function impairment, calcium channel dysfunction, and alternation in structural integrity. Most interestingly, when a "2nd hit" was administered such as brain injury or TBI in these mice, it led to an exacerbation of neuropathology and sustained deficits in cognition and behavior. The *Aldh2*$^{-/-}$ mice provides a model of early accelerated cognitive impairment where the basal level of susceptibility is increased which can be utilized with multiple 2 hits to mimic various diseases. The utilization of

this model allows us to define a “therapeutic window” and design varying paradigms for testing of potential therapies for TBI that may attenuate neuropathology and lead to beneficial strategies.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.21/BB16

Topic: C.09. Brain Injury and Trauma

Support: USAMRMC Combat Casualty Care Research Program H_024_2014_WRAIR

Title: Chronic behavioral deficits following traumatic brain injury combined with hypoxemic and hypotensive insults

Authors: *L. LEUNG, K. CARDIFF, X. YANG, S. BUTTLES, F. YANG, W. YANG, J. GILSDORF, D. SHEAR
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Severe traumatic brain injury (TBI) often results in long-term functional impairments, which may be exacerbated by additional insults such as respiratory distress and blood loss. The primary aim of this study was to determine the extent to which polytrauma, induced by hypoxemia (HX) and hemorrhagic shock (HS), may worsen neurofunctional outcome following penetrating ballistic-like brain injury (PBBI) in rats. Adult Sprague-Dawley rats were anesthetized and subjected to either 5% unilateral frontal PBBI or sham surgery. Groups were as follows: Sham control, HX+HS (HH), PBBI only, and PBBI+HX+HS (PHH). In HH and PHH groups, HX (P_aO_2=30-40mmHg) was initiated 5 minutes following PBBI or sham procedures and maintained for 30 minutes. After restoring normoxia, HS (MAP=40 mmHg) was initiated and maintained for 30 minutes. At 1-month and 3-month post-injury, motor function was assessed using the rotarod task and cognitive function was assessed using the Morris water maze (MWM) task.
PBBI animals displayed significant motor deficits on the rotarod task at 1-month post-injury vs. HH group, but not 3-months post-injury. In contrast, animals exposed to PBBI, HX and HS (PHH group) showed more sustained decrements in motor performance that were evident at both 1 and 3-months post-injury ($p<.05$ vs. HH group) and showed no improvement over time ($p>.05$ compared between 1- and 3-month performances). Significant spatial learning deficits were detected following PBBI alone at 3-months post-injury ($p<.05$ vs. sham and HH groups), and combined PBBI and HH insults at 1- and 3-month post-injury ($p<.05$ vs. sham and HH groups). While no significant difference in cognitive performance was detected between the PBBI and

PHH groups, there was a trend towards worsened outcome in the PHH group. Collectively, these results indicate that polytrauma induced by additional HX and HS insults resulted in early onset of chronic cognitive deficit and more prolonged impairment of motor function following PBBI. Better understanding of the chronic impact of TBI and additional insults provide a basis for therapeutic regimen aiming at promoting chronic recovery.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.22/BB17

Topic: C.09. Brain Injury and Trauma

Support: CHIR 39090-59420

CIHR 39654-59420

Title: Repeated mild traumatic brain injury impairs both spatial working memory and hippocampal synaptic plasticity

Authors: *C. PINAR-CABEZA, J. TRIVINO-PAREDES, C. J. FONTAINE, B. R. CHRISTIE
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Abstract: Traumatic Brain Injury (TBI) occurs when an impulsive force is transmitted to the head and affects the brain. While TBI is the leading cause of disability in individuals under 45 years of age, up to 75% of all brain injuries are classified as “mild” TBI (mTBI; also known as concussion). There is growing evidence that during a life time repeated mTBI can produce cumulative structural damage and long-term changes in behaviour. The juvenile brain is in a period of robust synaptic reorganization and myelination, making this a particularly vulnerable time to incur mTBI. The hippocampus is one brain structure that seems susceptible to mTBI and has been implicated in post-mTBI changes in cognitive and emotional processing. We have developed a new Awake Closed-Head Injury (ACHI) model that allows repeated mTBI to be studied in the juvenile brain. In the present study, we examined how animals responded after 8 ACHIs over a four day period in Long-Evans rats (25-28 days of age). Animals were assessed for changes in their state of consciousness and sensorimotor abilities immediately following each ACHI, allowing us to examine the acute effects of each injury. We also used a spontaneous alternation task to assess deficits in spatial working memory following the last ACHI. In conjunction with this, synaptic plasticity was assessed in littermates using *in vitro* electrophysiology either one day or seven days post-ACHI. Our results show that sensorimotor

abilities were affected after the injuries and that the ACHI model impairs both spatial working memory and hippocampal synaptic plasticity.

Disclosures: C. Pinar-Cabeza: None. **J. Trivino-Paredes:** None. **C.J. Fontaine:** None. **B.R. Christie:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.23/BB18

Topic: C.09. Brain Injury and Trauma

Support: Department of Veterans Affairs (RR&D Merit Review #B1097-I)

National Institutes of Health (NINDS T32-NS043126)

Title: Neurons in oculomotor nuclei are preferentially vulnerable following diffuse brain injury in swine

Authors: *C. KEATING[1,3], J. P. HARRIS[1,3], K. D. BROWNE[1,3], D. P. BROWN[1,3], J. E. DUDA[3,2], D. K. CULLEN[1,3]
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Abstract: Oculomotor deficits such as insufficiencies in accommodation, convergence, and saccades are a common occurrence following traumatic brain injury (TBI). Previous studies in patients with mild TBI have attributed these deficits to insufficient activation of subcortical oculomotor nuclei, although the mechanism for this dysfunction is unknown. Using a porcine model of closed-head rotational acceleration induced TBI that closely mimics the biomechanical etiology of diffuse TBI in humans – including all concussions – we previously reported acute plasmalemmal disruptions in neurons in the cerebral cortex and hippocampus. Building on these findings we hypothesize that neuronal populations in subcortical structures involved with oculomotor function will also preferentially exhibit plasma membrane damage following diffuse TBI. We tested this hypothesis using our established porcine model of head rotational TBI to investigate whether cell permeability changes occurred in subcortical oculomotor areas following single or repetitive TBI. Swine were subjected to sham conditions or head rotational acceleration (100-300 radians/second) in the coronal or sagittal plane using a HYGE pneumatic actuator. Two hours prior to the final injury, the normally cell-impermeant dye Lucifer Yellow (LY) was injected into the ventricles to assess plasmalemmal permeability. Animals were sacrificed 15 minutes after final injury for immunohistological analysis. Brain regions examined for neuronal permeability included the oculomotor nucleus (NIII), substantia nigra pars reticulata (SNpr),

caudate, and superior colliculus (SC). We found that the distribution of permeabilized cells varied depending on the plane of rotation and the number of injuries. Animals subjected to single head rotation in the coronal plane displayed the greatest incidence of neuronal permeability in NIII. Pigs subjected to single head rotations in the sagittal plane had the highest burden of neuronal permeability in SC. Animals subjected to repetitive head rotations had higher numbers of permeabilized cells in the SNpr compared to single rotations, with LY+ cells also observed in NIII and SC. The caudate did not contain permeabilized cells in following any injury paradigm. Current efforts are aimed at ascertaining the fate of injured neurons and their axonal projections from these mechanically vulnerable nuclei. Transient dysfunction and/or degeneration mediated by neuronal plasmalemmal disruptions within oculomotor nuclei may contribute to the symptomology of oculomotor deficits following diffuse TBI in humans.

Disclosures: C. Keating: None. **J.P. Harris:** None. **K.D. Browne:** None. **D.P. Brown:** None. **J.E. Duda:** None. **D.K. Cullen:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.24/BB19

Topic: C.09. Brain Injury and Trauma

Support: Psychological Health and Traumatic Brain Injury Research Program of the U.S. Department of Defense

Title: Controlled mild traumatic brain injury in a macaque animal model: Effects on contrast sensitivity and local cortical oscillations

Authors: *P. S. KHAYAT, R. FARIVAR-MOHSENI
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Abstract: Mild traumatic brain injury (mTBI) is a serious health problem, affecting more than 2 million North Americans every year, with common consequences of visual deficits such as blurry vision and lower contrast sensitivity. At a neural level, it has been hypothesized that mTBI changes the balance between local and global excitation/inhibition which affects the encoding of visual signals. Here, we developed the first macaque mTBI model to examine the neurophysiological consequences following local cortical trauma. Specifically, we asked whether mTBI changes cortical processing of visual inputs by recording local field potentials (LFPs) to gratings of varying contrast. In two animals, we induced controlled mTBI in small regions (5 mm) of the primary visual cortex using a magnetic impactor, and recorded LFP activity from 3-D neuronexus arrays that were smoothly implanted in the impacted sites and in non-impacted, control sites. We found that the LFPs contrast sensitivity was highly reduced in impacted sites,

which parallels the effects observed in mTBI patients. Noticeably, local mTBI in area V1 affected the pattern of neural oscillations, exhibiting significantly weaker stimulus-evoked oscillations in the gamma frequency range. Within the impacted V1 regions, neural activity was also weakly correlated compared to neighboring, control regions. These results show that mTBI changes the pattern of neural oscillations within the traumatic cortical region. These effects may result from changes in the balance between excitatory and inhibitory inputs into the traumatic site, decreasing the strength of the input drive into that region and leading to a reduction in visual sensitivity. The current study provides the first non-human primate model of mTBI to investigate its detrimental effects on neural processing and visual perception.

Disclosures: P.S. Khayat: None. **R. Farivar-Mohseni:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.25/BB20

Topic: C.09. Brain Injury and Trauma

Support: DePaul-RFUMS Alliance Pilot award

Title: Persistent upregulation of hippocampal synaptic transmission following repeated closed-head concussive impacts

Authors: *J. MCDAID[1], C. A. BRIGGS[1], A. LITTLEFIELD[1], N. KAPECKI[1], D. A. PETERSON[1], D. A. KOZLOWSKI[2], G. E. STUTZMANN[1]
[1]Dept. of Neurosci., Rosalind Franklin Univ., North Chicago, IL; [2]Neurosci. Program, DePaul Univ., Chicago, IL

Abstract: Traumatic Brain Injury (TBI) affects 1.7 million people annually and is a widespread clinical concern with long-term detrimental neurological and behavioral symptoms. TBI that doesn't result in obvious cell death or massive tissue damage is typically called "mild TBI" or concussion. Recently, much attention has been given to discriminating single concussion from repetitive concussion deficits , with repetitive concussion leading to worsened clinical symptoms, including memory loss and impaired thinking, which may be due to changes in hippocampal synaptic transmission and underlying neuro-inflammation. To assess the long-term effects of repetitive concussion on widely accepted mediators of learning and memory such as synaptic transmission and plasticity, calcium signaling and neuro-immune responses, we utilized a novel closed-head controlled cortical impact (CCI), a recently optimized approach which closely replicates the mode of injury in clinical cases. We also utilized a prolonged period of 30 days post-CCI to examine persistent effects of repetitive concussion and single concussion. Long Evans rats received a sham procedure (anesthetic) or a head impact at a location overlying the

sensorimotor cortex by a modified Leica CCI device. Experimental groups received a single impact or three successive impacts separated by 48 hour intervals. After 30 days, hippocampal slices were prepared for field recordings and whole-cell patch recording/2-photon Ca2+ imaging. Field recordings were performed in the CA1 dendritic layer using stimulation of CA3-CA1 Schaffer collaterals, with whole-cell patch/2-photon recordings performed on CA1 pyramidal neurons. Field recordings consisted of input-output functions and LTP induction. In repeat CCI rats, greater than 50% of slices had significantly increased synaptic responses when compared to single CCI or sham animals, indicating a sustained hyper-excitability in neuronal circuitry. Yet, no significant effects were observed on LTP expression or RyR Ca2+ responses, VGCC Ca2+ signals, input resistance, action potential properties or spontaneous EPSP frequency at this timepoint. Thus, repetitive concussion may lead to a unique and persistent upregulation of select excitatory hippocampal synapses through mechanisms yet to be uncovered, and these may contribute to the more detrimental long-term cognitive symptoms seen in repetitive concussion patients.

Disclosures: J. McDaid: None. **C.A. Briggs:** None. **A. Littlefield:** None. **N. Kapecki:** None. **D.A. Peterson:** None. **D.A. Kozlowski:** None. **G.E. Stutzmann:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.26/BB21

Topic: C.09. Brain Injury and Trauma

Support: FDA MCM 274

Title: Longitudinal electrophysiological signatures of mild brain injury in a mouse model

Authors: *M. YE[1], K. SOLARANA[1], S. PATEL[1], M. NABILI[1], S. HUANG[1], H. RAFI[1], J. A. FISHER[2], V. KRAUTHAMER[1], M. MYERS[1], C. WELLE[1,3]
[1]FDA, Silver Spring, MD; [2]Dept. of Physiol., New York Med. Col., Valhalla, NY; [3]Univ. of Colorado, Denver, Aurora, CO

Abstract: Currently there are no widely-used therapeutic medical products for mild traumatic brain injury (TBI), due in part to a lack of robust diagnostic markers for mild TBI. Improved quantitative measures for mTBI will facilitate the development of therapeutic treatments. As a direct reflection of brain function, electrophysiological indices have the potential to serve as a potent diagnostic marker for neural damage. Moreover, recent advances in electrophysiological recording technology allow for rapid, non-invasive signal detection on inexpensive and portable platforms. However, the characterization of the longitudinal dynamics of neural activity that accompany mild brain injury is incomplete. In this study, we identified electrophysiological

signatures of mild brain injury, and the temporal evolution of these markers, in a novel mouse model. The application of controllable high-intensity focused ultrasound (HIFU) pulses that mimic blast overpressure waves were used to produce a mild brain injury in mice. Chronic periodic brain activity recordings from freely moving animals were performed with a 16-channel epidural micro-electrocorticography (µECoG, Neuronexus) array implanted on the primary motor cortex. Spectral content and measure of neural synchrony were quantified throughout the injury and recovery process. Both acute and chronic electrophysiological indices differed between the injured and sham injury cohorts. Phase-amplitude coupling analysis demonstrated increased modulation of delta (1-4 Hz) phase on beta (13-30 Hz) amplitude within 2 days after the injury. Resting state brain oscillations had reduced absolute power in delta band and in the delta/gamma (30-100 Hz) ratio from 2 days to 4 months after brain injury. This change was accompanied by an increase in the broadband (1-100 Hz) mean frequency. No remarkable change was observed in coherence and entropy. Our data demonstrate that mild brain injury leads to both acute and chronic alterations in the spectral content and synchrony of cortical neuronal activity. The results may contribute to the use of electrophysiological indicators for the diagnosis of brain injury.

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Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.27/BB22

Topic: C.09. Brain Injury and Trauma

Support: CDMRP W81XWH-13-2-0019

CDMRP W81XWH-13-2-0018

CNRM HJF Award Number 307513-3.01-60855

Title: Linear mixed effects modeling of longitudinal *In vivo* diffusion MRI in the ferret brain following mild injury

Authors: *L. D. REYES[1,3], E. B. HUTCHINSON[1], N. SADEGHI[2], S. C. SCHWERIN[4], K. RADOMSKI[5], M. O. IRFANOGLU[1], S. L. JULIANO[6], C. PIERPAOLI[1]
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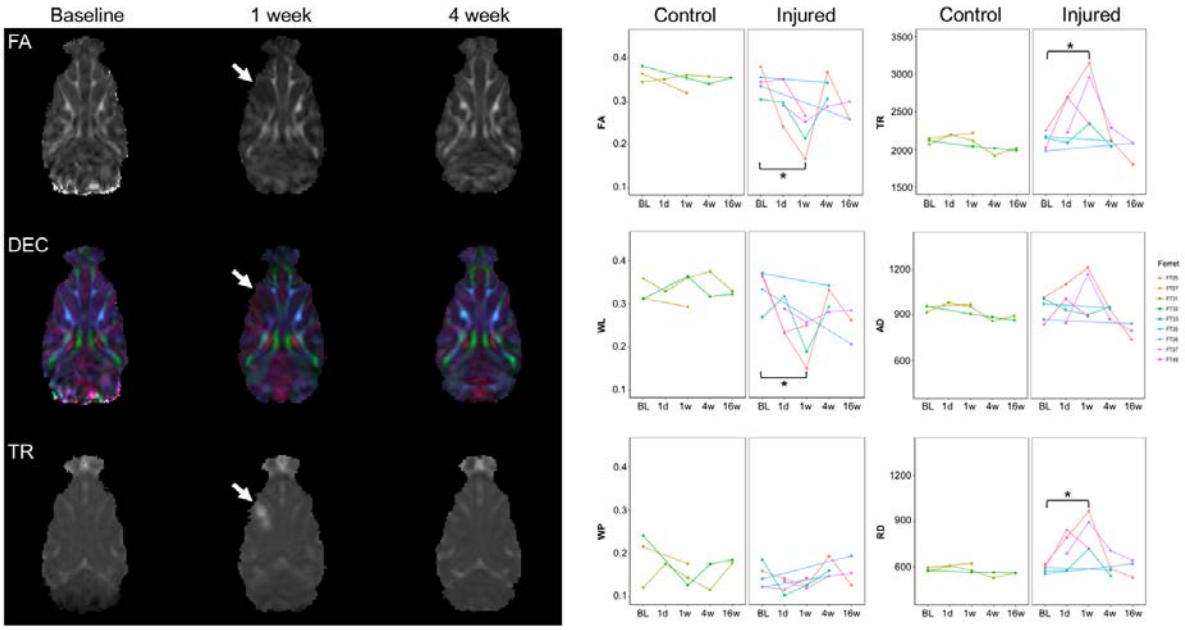
Univ., Bethesda, MD; [5]Ctr. for Neurosci. and Regenerative Med., Henry M. Jackson Fndn., Bethesda, MD; [6]USUHS, Bethesda, MD

Abstract: Identifying and evaluating imaging markers in Traumatic Brain Injury (TBI) remains a major challenge for the effective use of MRI as a clinical tool. This is evident with diffusion MRI, which can detect subtle abnormalities in mild TBI (mTBI). While *ex vivo* studies can reveal associations between MRI markers and pathology, these are limited to a cross-sectional design and do not take advantage of *in vivo* and longitudinal capabilities of MRI to capture TBI effects in single animals across time. Our goal was to assess if *in vivo* DTI can take advantage of a longitudinal design to identify mTBI markers in perilesional white matter.

We acquired longitudinal *in vivo* DTI scans from nine ferrets following mCCI (6 injured, 3 control) imaged prior to injury and variably at four time points post-injury: 1d, 1w, 4w, 16w. Single-shot 2D EPI was used to acquire isotropic diffusion weighted images with three b=0 images and 60 DWIs (b=700-1000 s/mm^2). Image corrections and DTI modeling was performed with TORTOISE and DTI maps were warped to a common template using the DR-TAMAS registration algorithm. We compared perilesional white matter values of fractional anisotropy (FA), Trace (TR), axial (AD) and radial (RD) diffusivity, and Westin linear (WL) and planar (WP) anisotropy maps using a linear mixed effects model (LME) that is robust to missing time point data and post-hoc pairwise comparisons using the lsmeans package in R.

The main results of the LME are shown in the figure. We found significantly lower values of FA and WL ($p<0.001$; $p<0.002$) and increased TR and RD ($p<0.008$; $p<0.002$) at 1w compared to baseline. FA, WL, TR, and RD returned to baseline levels at 4w. AD and WP did not show significant effects in perilesional white matter.

LME has enabled longitudinal assessment of tissue changes associated with mCCI to generate meaningful observations about longitudinal DTI in the ferret brain. As acquisition techniques improve, *in vivo* longitudinal animal imaging will become more widely available and LME along with DR-TAMAS registration methods are useful tools for ensuring high quality data analysis.



Disclosures: **L.D. Reyes:** None. **E.B. Hutchinson:** None. **N. Sadeghi:** None. **S.C. Schwerin:** None. **K. Radomski:** None. **M.O. Irfanoglu:** None. **S.L. Juliano:** None. **C. Pierpaoli:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.28/BB23

Topic: C.09. Brain Injury and Trauma

Support: W81XWH-13-2-0019

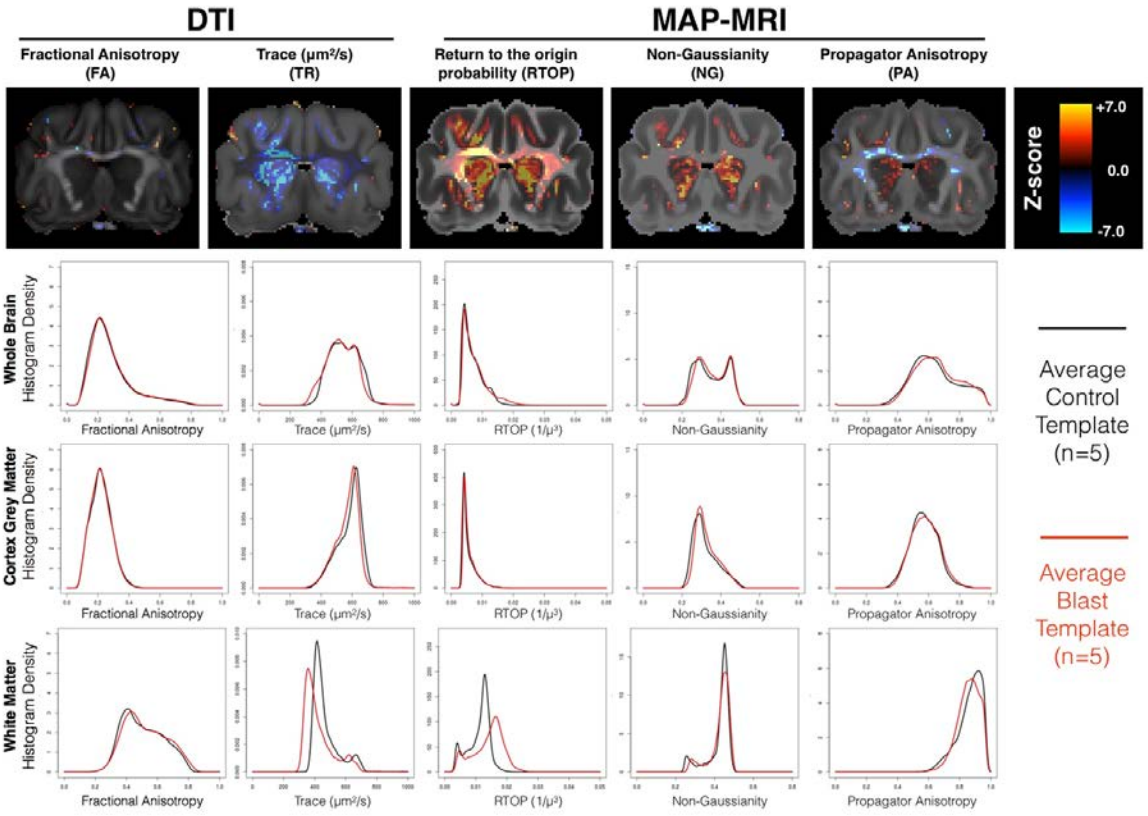
W81XWH-13-2-0018

Title: Detection of brain abnormalities following blast injury in the ferret by non-Gaussian diffusion MRI

Authors: *E. B. HUTCHINSON[1,3], S. C. SCHWERIN[4,3], A. V. AVRAM[2], M. O. IRFANOGLU[1], M. E. KOMLOSH[2,3], S. L. JULIANO[4], C. PIERPAOLI[1]
[1]Quantitative Med. Imaging Section, NIBIB, [2]Section on Quantitative Imaging and Tissue Science, NICHD, NIH, Bethesda, MD; [3]The Henry M. Jackson Foundation, Inc., Bethesda, MD; [4]Anatomy, Physiol. and Genet., Uniformed Services Univ., Bethesda, MD

Abstract: Traumatic brain injury (TBI) resulting from blast exposure is a relevant and poorly understood human condition and conventional MRI is often unable to detect brain abnormalities following blast. Diffusion MRI (dMRI) approaches are promising for their ability to probe the tissue structural environment by the 3D measurement and representation of water diffusion and advanced dMRI, which extends beyond diffusion tensor imaging (DTI), may offer improved detection of particular brain alterations after TBI, but they remain relatively untested for this purpose. In order to evaluate and compare DTI and non-Gaussian dMRI approaches for detection blast-TBI related brain abnormalities, high-resolution dMRI was performed in ex-vivo ferret brains 4 weeks following exposure to repeated blast. The ferret was selected for its human similar brain features of folded cortex and high white matter volume. Adult male ferrets were either untreated (n=5) or were exposed to 4 consecutive sessions of repeated blast (n=4) and four weeks later the brains were perfusion fixed and prepared for ex-vivo imaging at 7T. Diffusion weighted images (297) were acquired with 250 micron isotropic resolution and b-value=100-10,000 s/mm^2. DTI modeling was performed to generate maps for fractional anisotropy (FA) and Trace (TR) and mean apparent propagator (MAP) MRI was performed to generate maps for non-Gaussianity (NG), return to the origin probability (RTOP) and propagator anisotropy (PA). All metric maps were warped into a common space and Z-score maps were calculated to compare values from the injured brains to controls. Whole brain and tissue specific histograms were generated to compare metric values between the groups. Z-score maps and histograms are shown

in the figure and demonstrate several key findings: 1. The white matter is selectively vulnerable to blast injury, 2. RTOP and NG compared to Trace appear to offer distinct information (e.g. RTOP is stable in GM and NG is stable in WM, despite shifts in TR) and 3. While FA did not detect major abnormalities, PA was sensitive to decreased values in the white matter.



Disclosures: E.B. Hutchinson: None. **S.C. Schwerin:** None. **A.V. Avram:** None. **M.O. Irfanoglu:** None. **M.E. Komlosh:** None. **S.L. Juliano:** None. **C. Pierpaoli:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.29/BB24

Topic: C.09. Brain Injury and Trauma

Support: DoD/CNRM

Title: Random forests analysis of DTI metrics and histology measures in a mouse model of traumatic brain injury

Authors: *N. SADEGHI[1], E. B. HUTCHINSON[2], M. HABER[3], M. IRFANOGLU[2], L. D. REYES[2], C. PIERPAOLI[2]
[1]NICHD, [2]Quantitative Med. Imaging Section, NIBIB, NIH, Bethesda, MD; [3]Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Introduction:
Imaging markers provide crucial insight and important clinical tools for human brain injury. However, the relationship between imaging markers and pathomechanisms remains unclear. This study examines the sensitivity of diffusion tensor imaging (DTI) and quantitative histology measures to detect microstructural damage following experimental traumatic brain injury (TBI) in mice using random forest analysis (RFA) to identify the important regions and metrics affected by injury.
Method:
Paraformaldehyde fixed brain specimens were obtained from sham mice (n=5) and mice that were exposed to repetitive CHIMERA (Closed Head Impact Model of Engineered Rotational Acceleration) injuries (n=5).
Diffusion MRI data were acquired on a 14T Bruker system with a 3D echo-planar imaging acquisition with b-values= 250 to 3800 s/mm^2. The TORTOISE pipeline was used for image correction and tensor fitting. All diffusion tensors were registered to a common space using the DR-TAMAS registration algorithm. Diffusion parameters such as fractional anisotropy (FA), trace (TR), axial and radial diffusivity (AD, RD), Westin's linear and planar (WL, WP) were computed. In addition, quantitative histology values of percent area were measured in the same specimen with ImageJ to detect: axonal damage (APP), myelin damage (MBP), astrocytes (GFAP), and microgliosis (IBA-1). DTI metrics and quantitative histology measures for regions of interest (ROI) were used as input to RFA to classify injured tissue.
Results:
Using histology metrics, RFA was able to predict correct classification of all the injured animals, but wrongly classified one of the shams as injured, reaching an overall classification accuracy of 90%. Using a different combinations of DTI metrics (FA/TR, AD/RD, and WL/WP/TR), the same sham was consistently misclassified as injured and one injured sample was misclassified as sham reaching an overall classification accuracy of 80%.
Multiple DTI metrics as well as GFAP and IBA-1 of the optic tract and brachium of superior colliculus were consistently ranked as important for classification. Hippocampus was also ranked as an important ROI for classification using DTI metrics.
Discussion:
The study revealed that ex-vivo DTI abnormalities are evident post injury and RFA identified regions and metrics that can serve as potential imaging biomarkers. Multiple histological measures were affected in injured tissue indicating that multiple cellular processes affected DTI metrics. Nonetheless, RFA of DTI measures has proved to be a valuable tool for identifying injured regions and potential biomarkers for TBI.

Disclosures: N. Sadeghi: None. **E.B. Hutchinson:** None. **M. Haber:** None. **M. Irfanoglu:** None. **L.D. Reyes:** None. **C. Pierpaoli:** None.

Poster

140. Animal Models of Brain Injury: Anatomy, Physiology, and Pathology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 140.30/BB25

Topic: C.09. Brain Injury and Trauma

Support: DoD Grant W81XWH-16-1-0675

Title: Acute and chronic in-vivo electrophysiological changes following diffuse and focal traumatic brain injury in a large animal model of post traumatic epileptogenesis

Authors: *A. ULYANOVA[1], P. F. KOCH[1], C. D. ADAM[1], M. T. WEBER[1], D. K. CULLEN[1,2], B. LITT[1], D. H. SMITH[1], V. E. JOHNSON[1], H. I. CHEN[1,2], J. A. WOLF[1,2]
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Abstract: Traumatic brain injury is one of the largest causes of acquired epilepsy (post-traumatic epilepsy (PTE)). A prominent clinical question has been the relative contribution of diffuse and focal brain injury to the process of epileptogenesis. In this study, we are comparing porcine models of focal and diffuse injury and their contribution to epileptogenesis. Electrophysiological changes post traumatic brain injury (TBI) were first studied acutely in the inertial animal model of diffuse axonal injury (DAI). Male Yucatan miniature pigs (6 months) underwent coronal rotational acceleration (220-260 rad/sec), with little or no loss of consciousness. Laminar field potentials and single-unit activity were recorded in the dorsal hippocampus acutely 7 days post DAI. To precisely place silicone in-depth probes into porcine hippocampus, we have implemented non-imaging based stereotaxis and single-unit functional mapping. Laminar structure of the porcine hippocampus and the precise location of silicone probes were confirmed by electrophysiology and histopathology. In some animals, we observed induced sub-clinical epileptiform activity (sharp waves and paroxysmal depolarizing shifts), while principal cells and interneurons in pyramidal CA1 layer of all animals were affected differently based on waveform and firing rate analysis. These alterations suggest an increased post-synaptic excitability or a shift in the excitation-inhibition balance of the local circuitry. Over time post injury these changes may lead to circuit- level changes in the hippocampus and cortex that will elicit sub-clinical epileptiform activity and potentially lower seizure thresholds.
In order to monitor electrophysiological changes and to study this circuitry disruption in awake behaving pigs over time, we have developed and successfully implemented a Large Animal Custom Enclosure System (LACES), which consists of a 64-channel wireless recording system combined with custom 32-channels hippocampal depth probe and 32-channels cortical grid, along with ECoG probes placed in the contralateral hemisphere. This system allows for 24/7 video monitoring of animals, with alternate days of 24/7 monitoring of EEG, and is being

implemented in sham, contusion, rotational, and contusion plus rotational injury models for comparison of epileptogenesis in these injury types. A post-mortem examination of neuropathology will be performed, with emphasis on the temporal lobe connections. Circuitry changes, number and frequency of seizures and inter-ictal events will be correlated with the neuropathological outcomes to determine mechanistic underpinnings of PTE.

Disclosures: A. Ulyanova: None. **P.F. Koch:** None. **C.D. Adam:** None. **M.T. Weber:** None. **D.K. Cullen:** None. **B. Litt:** None. **D.H. Smith:** None. **V.E. Johnson:** None. **H.I. Chen:** None. **J.A. Wolf:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.01/BB26

Topic: C.09. Brain Injury and Trauma

Support: DoD Center for Neuroscience and Regenerative Medicine

DoD Program Project 308430 USUHS

Title: Synergistic interactions between TBI mechanisms and high altitude exposure

Authors: *N. P. CRAMER[1], A. KOROCTOV[2], A. BOSOMTWI[2], S. JAISWAL[2], X. XU[1], C. MEYER[2], K. WHITING[3], S. SHIVELY[4], D. IACONO[4], A. HOY[2], D. P. PERL[4], B. DARDZINSKI[2], Z. GALDZICKI[1]
[1]Anatomy, Physiol. and Genet., [2]Dept. of Radiology and Radiological Sci., [3]Neurosci. Grad. Program, [4]Dept. of Pathology, Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD

Abstract: Traumatic brain injuries (TBIs) have become a significant health problem for the Armed Forces, particularly those serving in high altitude (HA) combat environments. Service- and sport-related mild TBIs are mostly closed head injuries that are undetectable in the short-term but can produce significant neurological decline in the long-term. Operations conducted at HA expose the subjects to hypobaric-hypoxia which may adversely affect both the severity of TBI sustained in theater as well as the resulting neurological deficits. Using mouse models of HA exposure and repetitive closed-head TBI we investigated the potential interactions between mechanisms underlying TBI and targets of environmental stress triggered by hypobaric-hypoxia. After a 12 week acclimation to a simulated altitude of 5000 meters, mice that experienced three closed head injuries (CHI) showed significant deficits in the context component of a fear conditioning paradigm relative to HA shams and similarly aged sea level (SL) sham and CHI groups. Similar deficits were observed in the cued fear conditioning component although with less severity. In the open field test, HA mice tended to spend more time in the center zone

suggesting decreased levels of anxiety, while CHI mice, regardless of altitude exposure, traveled greater distances relative to shams. Longitudinal PET/CT and MR imaging of these mice showed bi-directional altitude dependent elevation of glucose metabolism varying by brain region and enhanced blood flow measures in cortex. Structural changes in brain vasculature related to altitude exposure and TBI were also observed. Analysis of imaging measures related to CHI-induced changes are ongoing. Together our results suggest that TBIs sustained in a HA environment result in greater behavioral deficits than those sustained at SL. Continuing analysis changes in vasculature and white matter deficit will establish, which pathological alterations may contribute to these behavioral changes. The final outcome of this study will help in better understanding of how trauma and environmental factors interact to cause disease states and will lead to novel approaches for the diagnosis, treatment and prevention of complex human disorders.

Disclosures: **N.P. Cramer:** None. **A. Koroctov:** None. **A. Bosomtwi:** None. **S. Jaiswal:** None. **X. Xu:** None. **C. Meyer:** None. **K. Whiting:** None. **S. Shively:** None. **D. Iacono:** None. **A. Hoy:** None. **D.P. Perl:** None. **B. Dardzinski:** None. **Z. Galdzicki:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.02/BB27

Topic: C.09. Brain Injury and Trauma

Support: Office of Naval Research Grant HU0001-15-2-0024

Title: Role of the gut brain axis, traumatic brain injury, and enteric infection on long-term behavioral and physiological outcomes in an animal model

Authors: *M. L. MEHALICK[1], F. POLY[2], M. PROUTY[2], R. MCCARRON[1,3], S. AHLERS[1]
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Abstract: The brain and the enteric system are intricately connected and together form the “gut-brain axis” (GBA). Within the GBA, there is bidirectional communication via neurotransmitters, hormones, and immune cells. When the brain is exposed to stress (e.g., from psychological or physical trauma), there can be physiological changes within the gut, and specifically within the composition and function of the gut bacteria. Similarly, a stressor to the gut, such as an enteric infection, can contribute to changes in brain function. The GBA can influence behavior, particularly anxiety and PTSD-like behavior. Blast-induced mild traumatic brain injury (mTBI) and enteric infections are common health concerns among military members in theatre. Together, these health concerns influence the GBA, and may influence behavior, especially the anxiety and

PTSD-like behavior that is often reported in service members returning from deployment. The goal of the current study was to assess how a physical trauma to the brain and an enteric infection may together impact long-term anxiety-like behavior. To simulate a blast-induced mTBI, rats were anesthetized and exposed to 75 Kpa (~10 psi) of blast overpressure from a blast tube once a day for three consecutive days. Approximately 24 hours after the final blast exposure, half of the animals were given a gavage of *Campylobacter jejuni* to induce an enteric infection. Four months after blast exposure and infection, anxiety behavior was assessed using the elevated zero maze and the light/dark emergence test. Rats exposed to both blast and Campylobacter infection were expected to show the greatest amount of anxiety compared to control animals or animals exposed to only blast or only Campylobacter. Contrary to hypotheses, animals exposed to both blast and Campylobacter showed less anxiety along with reduced levels of corticosterone compared to control animals. These results suggest that the long-term physiological effects of TBI and infection may be producing a stress habituation response, possibly via altered negative feedback loops, and thus animals are not as responsive to anxiety and stress.

Disclosures: M.L. Mehalick: None. **F. Poly:** None. **M. Prouty:** None. **R. McCarron:** None. **S. Ahlers:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.03/CC1

Topic: C.09. Brain Injury and Trauma

Support: New Jersey Commission on Brain Injury Research CBIR17PIL021

Title: Characterization of a combined model of blast and blunt injury

Authors: A. ARVIND, *B. J. PFISTER, R. KAKULAVARAPU, M. LONG, N. CHANDRA
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Abstract: Soldiers are often exposed to both primary blast waves and blunt impacts due to falls or vehicle crashes. While the cumulative effects of repeated exposure to a blast or blunt traumatic brain injury (TBI) has been under investigation, a combination of blast and blunt impacts has yet to be examined. Our hypothesis is a blast exposure, while not necessarily leading to a diagnosable injury, will predispose the brain to greater injury upon a second blunt injury to the head. Here, rats were exposed to primary blasts (130 KPa - mild or 180 KPa - moderate) followed by a moderate fluid percussion injury (FPI - 29-32 psi) to examine if a blast exposure would exacerbate the injury outcome of FPI in rats. The animals were first subjected to the blast then a craniectomy was performed while still under anesthesia and 24 hrs later, the rats were

subjected to the FPI. Control groups of blast +craniectomy, FPI only and craniectomy alone were also generated. Time-matched to 4hr after FPI, coronal sections from all experimental groups were stained with fluoro jade C. Acute neuronal degeneration was observed in the cortex, hippocampus and thalamus regions of the animals subjected to the blunt and blast +blunt group while blast alone group showed no neurodegeneration. Neurodegeneration was more pronounced in cortical region in the mild and moderate blast +blunt groups than the blunt impact group alone, while respective controls (blast +craniectomy or craniectomy alone) did not show any neuronal degeneration. Neuronal degeneration at the FPI site of impact was observed to be more pronounced in the mild blast+blunt group than the moderate blast+blunt group animals. Hemorrhage was also observed in the moderate blunt and combined impacts than the blast impacts. Potential changes in apnea and the righting reflex are so far inconclusive. Our data indicate that a prior blast impact increases the induced neuronal degeneration from a subsequent blunt impact. Ongoing studies aim to identify the longer term effects on cell death as well as behavioral and biochemical deficits present in the combined model.

Disclosures: **A. Arvind:** None. **B.J. Pfister:** None. **R. Kakulavarapu:** None. **M. Long:** None. **N. Chandra:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

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Program#/Poster#: 141.04/CC2

Topic: C.09. Brain Injury and Trauma

Support: Center for Neuroscience and Regenerative Medicine 3075113 10.01 60855

Title: Characterization of a mouse model of repetitive mild closed head injury

Authors: *N. C. SHANBHAG, Z. PAPADOPOULOS, A. J. SYMES
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Abstract: Closed head injury (CHI) models of traumatic brain injury are more reflective of the majority of traumatic brain injuries, yet result in fewer measurable behavioral or functional deficits. Repetitive injuries, which occur frequently in military personnel or athletes, often result in a more significant neuropathological phenotype. We have characterized a novel model of repetitive closed head injury (rCHI) in mice that produces substantial behavioral deficits, alterations in cerebral blood flow (CBF), glymphatic dysfunction and neuropathological changes. Adult male C57BL/6J mice received four moderate impacts to the head (+2.5mm left lateral, -2.5mm posterior to bregma; 5m/s velocity; 200ms dwelling time, 1.5mm depth; 5 mm impactor diameter; 14° to skin) under isoflurane anesthesia 24h apart, using an electromagnetically driven CCI impactor. Mice were sacrificed at 8, 28 or 56 days post injury (dpi). Mice after rCHI

exhibited hyperactivity and disinhibition, social withdrawal and abnormal nesting behaviour in comparison to sham injured animals. Behavioral changes were measurable for more than three weeks after injury. No major motor deficits were noted in this model. Intense immunoreactivity for GFAP and Iba1 revealed primary foci of injury beneath the impact site as well as at several secondary discrete sites. Fluoro-Jade C staining showed significant neuronal degeneration at 7dpi. Reactive astrogliosis and microglial activation were still evident up to 56dpi. CBF measurements using laser Doppler showed that CBF in the ipsilateral and contralateral hemispheres was significantly reduced at 1 and 3 dpi, in comparison to sham injured mice but recovered in both hemispheres by 7 dpi. Glymphatic function was measured by the distribution of fluorescent tracer injected into the cisterna magna 30 minutes before sacrifice. Injured animals showed a restricted distribution of tracer within the parenchyma in comparison to that in sham injured animals. This deficit was still detectable up to 56 dpi.
Our rCHI model shows significant behavioral deficits as well as alterations in glymphatic function and CBF, some of which persist several weeks after injury. Additionally, we detect prolonged glial reactivity. This model may therefore be useful for understanding therapeutic interventions to treat closed head injury.
Keywords: mice, repetitive, closed-head injury, cerebral blood flow, nesting, glymphatics, gliosis

Disclosures: **N.C. Shanbhag:** None. **Z. Papadopoulos:** None. **A.J. Symes:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Program#/Poster#: 141.05/CC3

Topic: C.09. Brain Injury and Trauma

Support: UC Irvine School of Medicine Faculty Research Grant

Title: Identification of brain regions activated during early coma recovery after resuscitation from cardiac arrest

Authors: *H. ABBASI, A. BAZRAFKAN, B. E. SHAMAOUN, T. WAIS, A. A. KHAN, Y. SURI, M. AZADIAN, S. M. ZAHER, F. AGUIRRE, G. TIAN, Y. AKBARI
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Abstract: Coma is a state of unconsciousness in which a person lacks wakefulness and awareness of their environment. One of the most common causes of coma is cardiac arrest (CA). After cardio-pulmonary resuscitation (CPR), the majority of CA survivors are in a state of coma. Arousal from coma is the #1 predictor of post-CA outcome, with quicker arousal strongly linked to improved long term outcome. How the brain recovers from deep comatose states, such as after

CA, remains unknown. Understanding which specific brain regions are involved in the earliest steps of coma recovery may have translational implications for patients suffering from coma. The expression of c-Fos, a well characterized “immediate early gene” (IEG), has been frequently used as an early marker of neuronal activity. We hypothesized that specific regions of the hypothalamus, thalamus, brainstem and cortex that are involved in arousal are also involved in the earliest stages of coma recovery and thus may exhibit c-Fos expression. Using an asphyxial CA+CPR model in rats (n=15), we compared c-Fos expression in brains of rats without CA (control) and compared with rats recovering after CA+CPR at different time points. At 2 hours post-CA, rats were comatose based on our behavioral test (neurological deficit scale) whereas by 24 hours, rats had nearly full arousal. In the 2 hour post-CA+CPR brains (in comparison to either control brains or 24 hour post-CA+CPR brains), we found higher levels of c-Fos expression in the hypothalamic and thalamic paraventricular nucleus (PVN), hypothalamic supraoptic nucleus (SON), thalamic central medial nucleus (CMN), and amygdala. Determining the function of the specific neurons in each of these nuclei involved in the earliest phase of coma recovery may have diagnostic and therapeutic implications for patients suffering from comatose disorders.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Program#/Poster#: 141.06/CC4

Topic: C.09. Brain Injury and Trauma

Support: VA RR&D CDA-2, RX-001479-01A2

Title: Effects of TBI on the limbic system in translational fear conditioning models of PTSD

Authors: *C. D. ADAM[1,3], R. J. RUSSO[1], J. C. ALAMAR[1], R. J. ROSS[3,2], V. E. JOHNSON[1], J. A. WOLF[1,3]
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Abstract: Traumatic Brain Injury (TBI) is considered the signature injury of recent US military conflicts, and Post-Traumatic Stress Disorder (PTSD) is a frequent comorbidity with TBI. Previous rodent models of TBI and PTSD have shown increased acquisition and decreased extinction of conditioned fear following TBI, as well as differential roles of the hippocampus (HC), basolateral amygdala (BLA), and medial prefrontal cortex (mPFC) in conditioned fear. However, the functional effects of TBI on these regions and how this leads to observed

behavioral changes are unknown. To better investigate this, both rodent and more translational large-animal models need to be utilized. This study sought to develop and characterize a robust fear conditioning (FC) model in pigs and characterize behavioral changes following TBI in both pig and rat FC models. This study also investigated structural and functional changes within and between the mPFC, BLA, and HC in pigs and rats that may underlie behavioral changes seen post-TBI. A rotational inertial model of TBI was used to induce a mild injury in pigs, and lateral fluid percussion was used to induce a mild to moderate (1.8-2.0 atm) diffuse TBI in rats. FC with pigs consisted of a day of acquisition followed by two days of extinction then reinstatement followed by two more days of extinction. During each day of FC, pigs were exposed to 10 presentations of 50ms pure-tone sound pips delivered at 1Hz for 30 seconds. During acquisition, each of the 10 presentations co-terminated with a mildly aversive electric stimulus. None of the presentations were paired during extinction, and only the 1st was paired during reinstatement. Heart rate was used as an outcome measure of fear. Pigs showed an increased heart rate during tone presentations (not correlated with movement) that dropped with each extinction, increased during reinstatement, then decreased again with later extinctions. Rats were either exposed to a FC paradigm similar to the one described above with pigs or to a differential FC paradigm where they were presented with two different auditory stimuli one of which co-terminated with a mild footshock (CS+) and one which was unpaired (CS-). Freezing was used as an outcome measure of conditioned fear. During extinction, injured rats had higher freezing rates than shams in the differential FC model, but lower freezing rates in the other FC model. Neuropathology as well as single-unit and local field potential electrophysiological recordings from bipolar microelectrodes and multi-site laminar probes in the HC, BLA, and mPFC are being used to investigate structure/function relationships underlying the neurophysiological basis of these TBI induced changes

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

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Program#/Poster#: 141.07/CC5

Topic: C.09. Brain Injury and Trauma

Support: American University of Beirut Medical Practice Plan

Title: Environmental Enrichment and Exercise affects memory and epigenetic events post severe traumatic brain injury

Authors: *H. J. DARWISH, N. RAMADAN, F. H. KOBEISSY
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Abstract: Severe Traumatic Brain Injury (TBI) survivors suffer from persistent cognitive deficits. Similarly, long-term recognition, temporal order, spatial learning and memory deficits follow experimentally induced severe TBI in rats. Therapies such as environmental enrichment (EE) and exercise are promising and enhance memory functions post severe TBI. However, few studies examined epigenetic, astrocytic changes in relation to memory functions after EE and exercise. Severe TBI using controlled cortical impact head injury in Sprague-Dawley rats will be used. After 14 and 21 days of EE coupled with daily exercise, spontaneous object recognition, temporal order and spatial learning and memory will be assessed using a Y-shaped maze and Morris water maze. Neurogenesis, epigenetic events and astrocytes changes will be measured using immunohistochemistry labeling and quantitative real time PCR. Decreased memory impairment and increase in neurogenesis in the experimental group compared to controls is expected; in addition to an elevation in the number of astrocytes as well as up-regulation in GFAP and Vimentin expression. Decreased DNA methylation and increased histone acetylation in the hippocampus are expected as well. Controlling and modifying the severe TBI survivors' environment as well as exercise to stimulate and restore sensory, motor and cognitive function is of a great clinical importance.

Disclosures: H.J. Darwish: None. **N. Ramadan:** None. **F.H. Kobeissy:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: FDA Medical Countermeasures Initiative (MCMi)

Division of Biomedical Physics lab funds

Title: Histological and behavioral characterization of a high-intensity focused ultrasound murine model of mild traumatic brain injury

Authors: *K. SOLARANA[1], S. PATEL[2], H. RAFI[1], S. MEHSUT[1], S. HUANG[1], M. NABILI[3], V. KRAUTHAMER[1], M. R. MYERS[1], C. G. WELLE[4], M. YE[1]
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Abstract: Traumatic brain injury (TBI) is a complex neurological condition experienced by 2.5 million Americans each year, many of whom also suffer from chronic secondary sequelae. Despite the high incidence of TBI, there exist no widely-used devices or drugs for treatment of

the condition. This is due, in part, to a lack of reliable biomarkers to identify and monitor this multi-factorial chronic condition. Mild TBI (mTBI), such as concussion, accounts for about 80% of all TBI and remains particularly enigmatic due to the low sensitivity of CT imaging and neurologic clinical assessment for mild injury. In order to study the complex pathophysiology of this disease and perform pre-clinical evaluation of the efficacy and reliability of potential diagnostic tools and neurotherapeutics, it is valuable to have a reproducible, scalable, and well-characterized animal model. Here, we applied high-intensity focused ultrasound (HIFU) pulse trains to intact skulls of mice *in vivo* to induce focal blast-related, non-impact mTBI of scalable severity. Locomotor impairments and changes in exploratory behavior following HIFU injury were assessed using rotarod and open field tests (OFT). The neuroinflammatory response to injury was then evaluated through immunohistochemical examination of astrocyte reactivity (GFAP) and microglial activation (Iba-1) throughout the brain at multiple post-injury time points. GFAP and Iba-1 staining densities have previously been shown to be elevated in several cortical and subcortical regions within 24 hours of HIFU-induced injury (McCabe, 2014). Our data, however, revealed large variation in histologically-assessed neuroinflammatory responses across animals within 24 hours, 1 week, and 7-months post-injury, but consistently poorer performance on neurobehavioral tasks in mTBI animals compared to sham-injured animals. Specifically, HIFU-injured animals showed a decrease in distance travelled in the OFT arena at 2 hours and 1 month post-HIFU, and a decreased ability to stay on the rotating rod at 2 hours, 24 hours, 1 week, and 1 month post-injury. Taken together, these results suggest that behavioral tests might be a more sensitive and reliable diagnostic measure than histological assessment of astrocyte and microglial activity in mild cases of focal TBI.
Disclaimer: The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Topic: C.09. Brain Injury and Trauma

Support: Start-Up Funds, University of Connecticut School of Medicine

Title: Axotomized adult retinal ganglion cells stimulated by extrinsic cues in a permissive environment survive and regenerate axons

Authors: B. A. RHEAUME, M. S. SAJID, *E. F. TRAKHTENBERG
Neurosci., Univ. of Connecticut Hlth. Ctr., Farmington, CT

Abstract: Retinal ganglion cells (RGCs) are projection neurons in the eye which, like other projection neurons in mammalian central nervous system (CNS), do not regenerate axons disrupted by an injury. The failure of axons to regenerate and restore long-distance connections between neurons limits recovery from ischemic or traumatic injury in the CNS. For example, blindness caused by trauma or stroke to the optic nerve disrupts the axons through which the RGCs pass information from the eye into the brain, resulting in irreversible blindness. Manipulation of various cell-autonomous and extrinsic factors have only partially restored axon regeneration in the CNS, and no clinical treatments exist to date that could help patients with axonal injuries. Thus, the failure of RGC and other CNS axons to regenerate after injury remains a major unmet problem. Here, we used bioinformatic analysis of RNA-seq transcriptome profiles of RGCs to predict extracellular matrix (ECM) molecules with which embryonic RGCs (that grow axons robustly) could interact, and then tested their effect in culture on RGCs isolated by immunopanning for Thy1.1. We found that not only did one of these ECM molecules (identity masked due to proprietary information) enabled axotomized adult rodent RGCs to survive for a long period, but also stimulated long-distance axon growth in a permissive culture environment. Thus, the identified ECM molecule holds potential for promoting axon regeneration after injury to the optic nerve, and perhaps other parts of the CNS as well.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Topic: C.09. Brain Injury and Trauma

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Steve Dunn Foundation

Coalition for Brain Injury Research

CONACYT-COPOCYT

Fundación Marrón Cajiga

Title: Differences in single and repetitive mild traumatic brain injury using different weights in a closed-skull weight drop model

Authors: *J. ALLENDE LABASTIDA[1], S. ALI[2], T. J. DUNN[1], J. GAO[1], D. S. DEWITT[3], D. S. PROUGH[3], P. WU[1]
[1]Neurosci. and Cell Biol., [2]Pharmacol. and Toxicology, [3]Anesthesiol., Univ. of Texas Med. Br., Galveston, TX

Abstract: Mild traumatic brain injury (mTBI) is an important public health problem, representing 75-87% of all TBIs. The collection of epidemiological information in single and repetitive mTBI (rMTBI) has proven to be challenging and it is severely underreported. Estimates suggest that only one in six single mTBIs are identified. Furthermore, specific groups, such as athletes and military personnel, have an increased risk of rmTBI and its consequences. However, pre-clinical *in vivo* models lack sufficient characterization and reproducibility to effectively study the sequelae of repetitive injuries. In order to obtain a better understanding of the forces involved in mTBI, we modified the weight drop model developed by Kane et al. in 2012 by adding a velocity sensor to calculate the kinetic energy applied towards the injury and monitor inter-injury variability. Different weights were used to determine optimal conditions to study rmTBI. Fifteen C57BL/6 mice (female, approximately 2.5 months of age) were randomly allocated in 5 groups: Sham, single mTBI with 95- or 120-gram weight (95x1 and 120x1), and rmTBI with 95- or 120-gram weights (95x5 and 120x5). Injury was performed using a 95 gram or 120 gram weights, dropped from one meter height. For repetitive injuries, animals were hit every 24 hours for 5 days. Elevated plus maze (EPM) test was conducted 3 days post injury and brains were collected on day 4 for immunohistochemical analyses. We observed a significant increase in righting reflex following rmTBI that follows a severity dependent manner. Additionally, the kinetic energy (joules) was calculated. There was a trend towards increased time spent in the open arms of the EPM that appeared severity dependent. Finally, we observed alterations in immunoreactivity of GFAP, APP and αSMA in multiple areas of the mice brains. These findings suggest that the closed-skull weight drop model using a120-gram weight at one meter height are better conditions to study rmTBI in our hands.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.11/CC9

Topic: C.09. Brain Injury and Trauma

Title: Effects of repeated closed head brain injury on attention and motor impulsivity

Authors: *H. BHATIA[1], C. E. CABRAL[1], C. W. IAMES[1], T. K. SHAVER[1], K. M. MARTENS[2], C. VONDER HAAR[1]
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Abstract: Traumatic brain injury (TBI) results in both immediate and chronic cognitive symptoms, such as impairments to impulse control abilities and attention. Milder closed head injuries have historically not been widely studied, and an understanding of their mechanisms are not well developed. The current study evaluated the effects of repeated closed head injury on attention and impulse control behaviors in rats.
Rats were trained on the five-choice serial reaction time test (5CSRT), an assessment of attention and motor impulsivity, until reaching a stable baseline (~60 sessions). Training took place in a bank of 16 operant chambers. On the task, animals were required to rapidly respond to the presentation of a brief (0.5 s) light stimulus in one of five holes (attentional component), but also withhold responding until the stimulus was presented (motor impulsivity component). Premature (impulsive), incorrect, and omitted trials were punished with a 5 s time out in which the houselight was illuminated. Sessions lasted for either 100 trials or 30 minutes. Once trained, injuries were delivered using the Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) system, with a 100 g, 5-mm impact tip centered just in front of bregma, delivered at 8 m/s. A total of thirty rats were separated into three cohorts. Ten received TBI twice/week (bi-Weekly TBI), ten received TBI once/week (Weekly TBI), and ten received sham procedures. Rats were continuously assessed for performance during the TBI period.
After three weeks of injuries, there were no alterations to attention or impulsivity in either Weekly or bi-Weekly TBI groups. These results stand in stark contrast to previous work showing deficits as a result of focal (open-skull) TBI. This suggests that injury severity as opposed to number of injuries is the primary driver of impulsive and attentional deficits. Future studies will identify the factors that underlie attentional deficits and increased impulsivity in order to better model human TBI.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.12/CC10

Topic: C.09. Brain Injury and Trauma

Title: Frontal traumatic brain injury reduces optimal decision making on a probabilistic reward task in rats

Authors: *B. ZHU[1], N. N. BERDAR[2], L. M. VELTRI[2], R. B. DALIDA[2], T. L. SCOTT[2], T. K. SHAVER[2], K. M. MARTENS[3], C. VONDER HAAR[1]
[1]Psychology, West Virginia Univ., Morgantown, WV; [2]West Virginia Univ., Morgatown, WV; [3]West Virginia Univ., Morgantown, WV

Abstract: Traumatic brain injury (TBI) is a major public health concern with a high rate of psychiatric comorbidities. Patients with brain injury tend to have severe and long-lasting neurological and cognitive deficits. A major post-injury problem is increased impulsivity which may also contribute to risky decision making. The current study focused on evaluating the effects of frontal TBI on risky decision making in rats.
Forty-seven rats (23 sham and 24 injured) were trained on the Rodent Gambling Task, an analog of the Iowa Gambling Task that is used to assess decision making in humans. Training took place in a bank of 16 operant chambers. Rats were presented with choice of four different options, with each option associated with a specific probability of reward (sucrose pellets) or punishment (time out). The probabilities were arranged such that two options provided a low-risk, but low-reward profile, while the other two provided a high-risk, high-reward profile. Choice of the low-risk options lead to maximal sugar pellets earned within a 30-minute session. Rats received either bilateral, frontal controlled cortical impact injury (+3.0, +0.0, -2.5 @ 3 m/s) or sham procedures (craniotomy or intact sham). After one week of recovery, the rats were tested on the Rodent Gambling Task. One-half of the animals were tested in acquisition (no prior experience with the RGT) or at steady-state performance (statistically stable behavioral baseline) to compare TBI-induced alterations to learning versus learned behaviors.
TBI resulted in substantial alterations to choice, both in steady-state and acquisition animals. Specifically, TBI reduced choice of the most optimal option in steady-state animals, with a slow recovery towards baseline behavior. TBI also altered acquisition of choice and animals demonstrated slower learning, and lower preference for the most optimal option. Sham animals showed no detectable alterations to either steady-state or acquisition performance. This study shows that TBI-induced alterations to decision making can be modeled in rodents, and provides a strong method for assessing novel therapeutics aimed at treating psychiatric-like deficits after brain injury.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Program#/Poster#: 141.13/CC11

Topic: C.09. Brain Injury and Trauma

Title: Combining force and rotation in TBI: The creation of a novel device for translational traumatic brain injuries

Authors: *W. R. KOCHEN, *W. R. KOCHEN, K. M. CRAVEN, D. D. CERRI, J. M. FLINN
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Abstract: Traumatic Brain Injuries (TBI) affect approximately 2 million people every year and have devastating long term effects. TBIs comes from a variety of sources including falls, blast injuries, and sports related hits to the head. Many of these injuries occur with the blow to the head being followed by a fall to the ground. It is thought that the rotation and fall following the injury contribute to the pathology seen in TBIs; however, most models of brain injury do not contain both an injury and a rotational fall. We sought to create a modified brain injury apparatus that allows for the animal to be struck in the head and then experience a rotational fall. The device consists of an elevated platform on which the mouse is placed. A sensor connected to the machine will cause the platform to drop after the injury. This device allows for the severity of injury and delay between injury and fall to be modified. This apparatus is built on top of a stereotax and our model uses a Leica CCI device but would work with most available products for inducing injury. Some rotational fall paradigms exist already and have been shown to produce a more translational model of injury. An advantage to this new apparatus is it modifies a very common method of injury so that it could be affordably added to many labs' devices; this allows for the production of a rotation added to an injury of any range from concussive to severe injury.

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Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Topic: C.09. Brain Injury and Trauma

Title: Social isolation after repetitive mild traumatic brain injuries

Authors: *K. M. CRAVEN, W. R. KOCHEN, D. D. CERRI, J. M. FLINN
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Abstract: Traumatic Brain Injuries (TBIs) affect nearly 2 million individuals each year, with many of these injuries being mild (mTBI). These injuries affect athletes and soldiers, and are also very common in adolescents. Often times, individuals that sustain a TBI have long recovery periods, memory impairments, and difficulty carrying out everyday tasks. This experiment examines if social isolation exacerbates the effects of repetitive mTBIs. Adolescent mice are

utilized and injuries are given using a novel TBI method that has been developed in our lab. Our method utilizes a platform that falls once an impact occurs, mimicking the rotational effects after a TBI. Mice sustain a closed-head mTBI once every day for five days. Half of the mice are socially isolated until the end of the experiment by placing them in a home cage by themselves. Spatial memory is assessed using the Barnes Maze and anxiety is assessed using Elevated Zero. Tests of general well-being including nesting, burrowing, and circadian rhythm are also conducted. It is hypothesized that socially isolated mice will show spatial memory deficits, higher levels of anxiety, and poorer overall well-being.

Disclosures: K.M. Craven: None. **W.R. Kochen:** None. **D.D. Cerri:** None. **J.M. Flinn:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 141.15/CC13

Topic: C.09. Brain Injury and Trauma

Support: CDC-NIOSH NORA Intramural Grant

Title: Development of a preclinical rodent model for closed-head non-fatal work-related traumatic brain injury

Authors: *J. V. MILLER[1], B. M. WIMER[2], K. A. KELLY[1], L. T. MICHALOVICZ[1], C. S. PAN[2], J. P. O'CALLAGHAN[1], D. B. MILLER[1]
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Abstract: Traumatic brain injury (TBI) has quickly become one of the major causes of death and disability in the United States. With the vested interest in TBI research for sports-related injuries, many advances have been made in the sports arena that can guide preventative and protective measures for athletes. However, until a few years ago, TBI in the workplace had not been well documented. Most non-fatal work-related brain injuries are due to contact with objects and equipment and falls. The rate of non-fatal work-related TBI has continued to increase over the last 20 years, but factors contributing to TBI susceptibility or outcome have not been fully elucidated. Animal models for TBI offer a unique opportunity to test a variety of factors in a controlled and reproducible environment. To this end, we utilized the Walter Reed Army Institute of Research (WRAIR) projectile concussive impact (PCI) model of mild TBI to develop a rat model for non-fatal work-related TBI and evaluate the acute effects of PCI closed-head injury in rats. In this study, male Sprague Dawley rats were exposed to a single PCI (3/8" stainless steel ball bearing traveling at 75 ± 5 ft/sec) while anesthetized and wearing a custom carbon fiber helmet. The carbon fiber helmet absorbed most of the delivered force, as evidenced by pressure film recordings on the exterior and interior of the helmet. Rats were sacrificed at 24,

48, and 72 h after PCI for histological analyses. Histology revealed an increase in microglial activation over time and slight increase in neurotoxicity. Rats were sacrificed at 72 h for RNA-sequencing (RNAseq) analysis of the posterior cortex, which lays beneath the region of the skull where the PCI was delivered. RNAseq revealed adequate helmet protection with few significantly differentially expressed genes when compared to control. These results suggest that our rat model for non-fatal work-related TBI can be a critical tool for elucidating factors contributing to susceptibility and outcome of non-fatal work-related TBI.

Disclosures: J.V. Miller: None. **B.M. Wimer:** None. **K.A. Kelly:** None. **L.T. Michalovicz:** None. **C.S. Pan:** None. **J.P. O'Callaghan:** None. **D.B. Miller:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

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Program#/Poster#: 141.16/CC14

Topic: C.09. Brain Injury and Trauma

Support: ABRC(ADHS14-000003606)

VRP(P1201607)

PCH Director’s Fund

Title: Alterations to the central nucleus of the amygdala following traumatic brain injury coincide with late-onset affective symptoms

Authors: *J. A. BEITCHMAN[1,2,3], D. R. GRIFFITHS[1,2], Y. HUR[1,4], P. D. ADELSON[1,2], J. LIFSHITZ[1,2,4,5], T. C. THOMAS[1,2,5]
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Abstract: Affective symptoms, including anxiety and post-traumatic stress disorder, are reported in up to 50% of traumatic brain injury (TBI) survivors. Etiology underlying these affective symptoms remain unknown which often makes treatment options imprecise and ineffective. The central nucleus of the amygdala has been shown to regulate responses to negative stimuli and anxious behaviors. We therefore hypothesized experimental diffuse TBI produces functional and structural alterations to the central nucleus of the amygdala (CeA) as possible explanations for late-onset affective symptomatology. Adult, male Sprague-Dawley rats were subjected to midline fluid percussion injury or sham surgery. Anxiety-like behavior was assessed using open-field at 1 week or 1 month post-injury. Immediately following testing, microelectrode arrays placed in the CeA of anesthetized rats quantified real-time glutamatergic neurotransmission as an

index of CeA function. CeA structure was evaluated histologically by silver and GFAP stains to assess neuropathology and astrocytosis. We found brain-injured rats spent significantly less time in the center of the open-field compared to shams at 1 month but not 1 week post-injury. Additionally, brain-injured rats non-significantly decreased distance traveled and made significantly fewer entries to the center of open field at 1 month post-injury compared to shams. This late-onset anxiety-like behavior coincided with significant alterations to glutamate neurotransmission. One month brain-injured rats had significantly less evoked glutamate release compared to shams. Evaluations of glutamate clearance revealed 1 week and 1 month brain-injured rats had significantly slower glutamate uptake rates. Preliminary assessment of CeA structure showed no changes in neuropathology following brain-injury compared to shams. Together, diffuse TBI resulted in late-onset, anxiety-like behavior coincided with altered CeA glutamate neurotransmission and no changes to neuropathology. Subsequent studies of glutamate receptors and transporter levels in the CeA may identify molecular mechanisms contributing to the observed alterations in glutamate neurotransmission. These data are the first to demonstrate that experimental diffuse TBI causes alterations in glutamate neurotransmission within the CeA that coincide with late-onset anxiety-like symptoms. Mechanisms that contribute to altered glutamate neurotransmission in the amygdala may be a plausible therapeutic targets to alleviate affective symptoms for TBI survivors.

Disclosures: J.A. Beitchman: None. **D.R. Griffiths:** None. **Y. Hur:** None. **P.D. Adelson:** None. **J. Lifshitz:** None. **T.C. Thomas:** None.

Poster

141. Brain: Animal Models of Brain Injury and Behaviors

Location: Halls A-C

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Program#/Poster#: 141.17/CC15

Topic: C.09. Brain Injury and Trauma

Title: Stereotypical-like behavior following traumatic brain injury in mice

Authors: *J. POPOVITZ, H. ADWANIKAR
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Abstract: Traumatic brain injury (TBI) increases the risk of psychiatric disorders including anxiety, depression, and compulsions. In animal models, grooming is a behavioral class which serves, among other things, as a model for stereotypical responses, and as a de-arousal mechanism after stress exposure. Duration, pattern, and length of episodes are all markers of grooming behavior that allow distinction between stereotypical and anxiety-dependent grooming response. While previous studies have measured anxiety-like behaviors in mice models of traumatic brain injury, the changes in stereotypical behavior are not well understood. In this study, we measure grooming behavior for eight weeks following controlled cortical impact

injury in mice. We quantitatively assess duration, length of episode, number of episodes, rostro-caudal pattern and sequencing of grooming behavior. Additionally, we also evaluate anxiety metrics within these animals over the same time frame. Together, these metrics allow us to evaluate if TBI produces aberrant grooming behavior, and whether observed changes are indicative of rigid behavior commonly associated with compulsive disorders, or disorganized sequencing suggestive of an increased anxiety state. In parallel, we evaluate volumetric and molecular correlates within the corticostriatal pathway to examine potential neural correlates of changes in stereotypical behaviors. These results will start to address the link between TBI and compulsive-like disorders.

Disclosures: J. Popovitz: None. **H. Adwanikar:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 142.01/CC16

Topic: C.09. Brain Injury and Trauma

Support: Craig H. Neilson Foundation (191152)

Title: Longitudinal electrical stimulation training of the lower limbs: Changes in neural control of postural stability

Authors: *K. MOMENI[1,2], A. RAMANUJAM[1], E. L. GARBARINI[1], G. F. FORREST[1,2]
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Abstract: After spinal cord injury (SCI), there is often impairment of function below the lesion level. We have published that multi-muscle electrical stimulation (ES) combined with stand training (ST) could increase: i) neuromuscular control below the lesion level, and ii) overall postural stability during long bouts of stepping. The purpose of the present study was to examine the continuum of ES training for 120 hours. The first 60 hours of training involved ES alone with no task-specific loading. The second 60 hours of training involved ES with task-specific loading during the stimulation. Neuromuscular improvements for trunk independence and trunk stability parameters were evaluated during standing and during a 10-minute continuous stepping on a treadmill using body weight support with overhead harness. Two-dimensional spatial and temporal profiles of trunk Center of Mass, as well as the underlying neural changes to trunk anterior and posterior muscle groups precipitating the alterations in postural mechanics were examined. Our results revealed that the first 60 hours increased static trunk stability and standing independence during a quiet standing period. The second 60 hours of training continued to increase trunk independence during standing and importantly increased trunk neural control and

trunk independence during a continuous 10-minute stepping period. The continuum of 120 hours of ES highlighted the significance of task specificity of loading on the neural motor pools.

Disclosures: K. Momeni: None. **A. Ramanujam:** None. **E.L. Garbarini:** None. **G.F. Forrest:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Topic: C.09. Brain Injury and Trauma

Support: NJ Commission on Spinal Cord Research Grant - CSCR14ERG007

Title: Assessing the muscle activations during volitional effort with and without electrical stimulation through surface electromyograms

Authors: *R. PILKAR, A. RAMANUJAM, E. GARBARINI, G. F. FORREST
Human Performance and Engin. Res., Kessler Fndn., West Orange, NJ

Abstract: Functional electrical stimulation (FES) has been used to assist or restore neuromuscular function to paralyzed muscle after spinal cord injury (SCI). During FES, electrical current is applied to a nerve to elicit action potentials in denervated peripheral muscles. Chronic application of FES have been shown to have therapeutic effect on tissue health or voluntary function to some extent. Surface electromyography (EMG), otherwise an effective tool to analyze underlying muscle activity, limits the assessment of the direct effect of FES on a muscle or nerve due to the presence of overpowering stimulus artifact. Recent advances in biomedical signal analysis have yielded algorithms that show significant success in removing electrical stimulation (ES) artifacts from EMG recorded from the stimulated muscle. In this study, we used the empirical mode decomposition (EMD) with Notch filtering based approach to remove ES artifact from EMG of the stimulated (35 Hz, 300μs) rectus femoris (RF) muscle. With this, we clearly showed distinguishable, artifact-free, muscle activations during ‘only ES’ and ‘ES combined with volitional effort (ES+VOL)’ conditions in individuals with a SCI (n=2) and able bodied (n=5) participants. In this study, we assess the intrinsic characteristics of EMGs (amplitudes, frequency etc.) during ‘only VOL’ and ‘ES+VOL’ while maintaining a predefined level of effort (measured by force). Moreover, the artifact-free EMGs could also provide a way to quantify the individual contributions of volitional and ES components to achieve/maintain a certain level of effort. This information could be important in designing FES interventions that combine volitional effort to achieve a functional task in individuals with neurological or musculoskeletal impairments.

Disclosures: **R. Pilkar:** None. **A. Ramanujam:** None. **E. Garbarini:** None. **G.F. Forrest:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Program#/Poster#: 142.03/CC18

Topic: C.09. Brain Injury and Trauma

Support: NJCSCR

CHNF

Title: Patterns of stimulation effect on muscle volume

Authors: ***G. F. FORREST**[1], E. REJC[2], A. RAMANUJAM,[1], E. GARBARINI[1], S. J. HARKEMA[3]
[1]Kessler Fndn., West Orange, NJ; [2]Univ. of Louisville, Louisville, KY; [3]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Acute spinal cord injury often leads to rapid muscle atrophy in the paralyzed limbs. We have shown that an intense novel form of multi-muscle neuromuscular electrical stimulation using traditional stimulation parameters combined with dynamic stand retraining task may potentially restore muscle volume, structure and function after sub acute to chronic, motor-complete SCI. Furthermore we have shown an increase in activation in flexor and extensor motor pools of the lower limbs as a result of task specific training.
More recently we have shown that different parameters of stimulation can influence the change in overall total muscle cross sectional area/volume in the lower limbs. However, little is known as to how these parameters affect the flexor and extensor muscle cross section of the lower limb. We will present data for individuals with a sub acute to chronic cervical and thoracic, motor complete spinal cord injury who have undergone longitudinal training for a large number of standardized task specific training sessions with bilateral multi muscle neuromuscular electrical stimulation of the flexors and extensors of the lower limbs to compare different parameters of stimulation of the lower limb muscle for changes in total limb muscle CSA/volume/strength. Muscle volume will be presented for bilateral thigh and shank muscles. Muscle strength will be determined for flexors and extensors of the lower limbs. Moreover we will present cross sectional area data for slices for the total limb as well as flexors and extensors of the compartments of the lower limb.

Disclosures: **G.F. Forrest:** None. **E. Rejc:** None. **A. Ramanujam,:** None. **E. Garbarini:** None. **S.J. Harkema:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Support: GM103507

NS089324

Kentucky Spinal Cord and Head Injury Research Trust

Norton Healthcare

Commonwealth of Kentucky Challenge for Excellence

Title: Taking strides towards recovery: Silencing long ascending propriospinal neurons improves locomotor outcomes after spinal cord injury

Authors: *C. T. SHEPARD[1,2,3], M. A. VAN RIJSWIJCK[3,4], A. M. POCRATSKY[2,3], N. D. SPICER[3,4], A. S. REIGLER[3,5], S. R. WHITTEMORE[1,2,3,5], D. S. MAGNUSON[1,2,3,4,5]
[1]Interdisciplinary Program in Translational Neurosci., [2]Anatom. Sci. & Neurobio., [3]Kentucky Spinal Cord Injury Res. Ctr., [4]Bioengineering, [5]Neurolog. Surgery, Univ. of Louisville, Louisville, KY

Abstract: Central patterns generators (CPGs) are neuronal networks that generate coordinated limb movements associated with stepping. However, the functional roles of discrete pathways associated with locomotor CPGs after spinal cord injury (SCI) are poorly understood. In the mammalian spinal cord, long ascending propriospinal neurons (LAPNs) are part of an inter-enlargement population of neurons that interconnects the hindlimb and forelimb CPGs in the cervical and lumbar enlargements, respectively. LAPN axons likely remain intact after SCI as their axons travel in the peripheral aspects of the lateral and ventral white matter, tissue that is often spared following SCI. Previously, we reversibly silenced synaptic transmission of LAPNs in uninjured female Sprague Dawley rats and demonstrated a disruption of right-left alternation of the hindlimbs and forelimbs during overground stepping. Importantly, the fundamental relationships between stance and swing parameters and speed (spatiotemporal measures) were preserved during LAPN silencing. Based on these data, we hypothesized that conditional silencing of LAPNs after spinal cord injury would result in diminished hindlimb locomotor function. To test this hypothesis, we examined the animals' gait and kinematic measures, as well as BBB scores with and without silencing after spinal cord injury. Surprisingly, silencing LAPNs post-SCI restored the spatiotemporal relationships and left-right temporal relationships associated with alternating gaits that were lost after SCI, leading to improved overall locomotor

function. These functional improvements were further validated by changes in the BBB scores. These data suggest that removal of inaccurate or incomplete temporal information from the below the level of injury may lead to improvements in locomotor function. Clinically, this has important implications as methods of spinal cord excitation and stimulation are currently being used to illicit improvements in standing or stepping in SCI patients. It is critical to consider that intact and partially spared pathways may be communicating disruptive information throughout the system, which may be limiting the recovery potential of SCI patients.

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Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: Swiss National Science Foundation

European Research Council (ERC) advanced grant (Nogorise)

Christopher and Dana Reeve Foundation

Title: Voluntary movement control under deep brain stimulation of the mesencephalic locomotor region in rats is dependent on stimulation intensity

Authors: *A.-S. HOFER, J. MAEDER, A. M. SARTORI, A. K. ENGMANN, N. RUSSI, M. E. SCHWAB
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Abstract: Incomplete spinal cord injury, characterized by sparing of supraspinal projections, affects millions of people worldwide. Loss of motor function and locomotion is common, even in patients who retain some degree of leg muscle control. A small group of neurons in the pedunculopontine and cuneiform nuclei of the midbrain tegmentum, i.e. the mesencephalic locomotor region (MLR), is well known to initiate and control locomotion mostly using an indirect relay via ipsi- and contralateral reticulospinal nuclei. Electrical deep brain stimulation (DBS) of the MLR using the brain´s intrinsic motor command circuits was suggested as a novel treatment strategy to induce recovery of locomotor functions in rats with subtotal spinal cord lesions (Bachmann et al., Science Translational Medicine, 2013).
In order to consider DBS of the MLR as a potential therapeutic treatment option for incompletely lesioned patients, it needs to be evaluated whether DBS facilitates the re-establishment of physiological movement patterns that are still under voluntary movement control.

To investigate voluntary movement control under MLR-DBS, we stereotaxically implanted DBS electrodes unilaterally into the MLR of rats. Subsequently, the animals underwent testing of voluntary movement control in different behavioral setups, e.g. a T-maze, where a left turn decision has to be made, and an open field with obstacles to test obstacle avoidance. While the absolute intensity of effective stimulation strength varied between individuals, obstacle avoidance and correct T-maze choices were consistently observed at lower and intermediate stimulation strength. Pilot study data showed that at stimulations >75% of maximal effective strength, rats started to lose voluntary control over their movements. These results suggest that MLR stimulation, within defined intensity ranges, can enhance physiological movement patterns under full cerebral control.

Disclosures: A. Hofer: None. **J. Maeder:** None. **A.M. Sartori:** None. **A.K. Engmann:** None. **N. Russi:** None. **M.E. Schwab:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: Leading Talents of Guangdong Province Grant 87014002

Title: Controlled release of growth factors from functional self-assembling peptide nanofiber hydrogels for endogenous neural regeneration in spinal cord

Authors: *X. XU[1], L. HE[2], H. LIU[1], C. LI[1]
[1]Guangdong-hongkong-Macau Inst. Of Cns Regenera, Guangdong, China; [2]Key Lab. of Biomaterials of Guangdong Higher Educ. Institutes, Dept. of Biomed. Engineering, Col. of Life Sci. and Technolog, CuangZhou, China

Abstract: Endogenous neural stem cells(eNSCs)play an important role in the adult mammalian central nervous system(CNS)for neural regeneration through appropriate activation, differentiation, maturation, and forming new neural network. However, the CNS injury environment and inflammatory are harmful to eNSCs. In this study, proposed to create a permissive microenvironment for eNSCs by functional self-assembling peptide nanofiber hydrogels loaded growth factors "cocktail". eNSCs activation, immigration and differentiation were thoroughly investigated. The motor tract was detected by biotinylated dextran amine (BDA, 10KDa) anterograde tracing. AAV-retro/GFP that was injected into sciatic never were used to conform sensory-motor tract regeneration. Moreover, at the mercy of the hind limb muscle, the gastrocnemius muscle be infected with pseudorabies virus (PRV-GFP). The behavior recovery was studied by BBB locomotion assessment. Two weeks after injury, axon regeneration was

obviously observed with many newly born neurons. Two months later, motor and sensory tracts were significantly reestablished. Hind limb functions were significantly improved as compared with the rats without interventions. Therefore, our study documented a feasible strategy for neural regeneration after spinal cord injury by presenting a permissive environment for endogenous neural regeneration.

Disclosures: **X. Xu:** None. **L. He:** None. **H. Liu:** None. **C. Li:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Program#/Poster#: 142.07/CC22

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH R01 NS064004

Title: Chronic M1 optical iTBS produces axonal outgrowth and strengthens connections in the corticospinal system

Authors: *L. YANG[1], J. H. MARTIN[1,2]
[1]CUNY Sch. of Med., New York, NY; [2]The Grad. Ctr. of CUNY, New York, NY

Abstract: Activity-dependent plasticity plays an important role in learning and memory, leading to strengthening of highly active synapses and, through mechanisms of activity-dependent competition, pruning of less used connections. In the corticospinal system and motor cortex (M1) of rodents, we have shown that electrical stimulation promotes corticospinal tract (CST) axonal outgrowth and, after injury, further outgrowth and recovery of forelimb function. For the CST, it is not known if the absolute level of neuronal activity is critical or if the relative level of activity in neighboring populations is important. We hypothesize that increased activity leads to selective outgrowth in stimulated axons and confers a competitive advantage over less active neighboring axons.
To investigate the effect of chronic stimulation on activated neurons, as well as the interaction between highly active axons and their less active neighbors, we used an optogenetic approach to selectively activate channelrhodopsin-expressing (ChR2+) axons in the CST of adult rats. We injected AAV-ChR2-EYFP and control AAV into partially overlapping sites unilaterally in forelimb M1. ChR2-labeled axons were optically stimulated 30 mins daily for 10 days following an iTBS protocol. After 10 days of stimulation, we performed a terminal M1 mapping experiment (ICMS), after which animals were perfused and tissue collected for anatomical analyses.
ChR2+ axons showed substantial axonal outgrowth and branching compared to control axons (AAV only), in both the ipsilateral and contralateral spinal cord. More ChR2+ axons extended

into forelimb motor nuclei than control axons. Thus, chronic optical iTBS stimulation in uninjured animals produces morphological changes specific to stimulated axons. The synaptic morphology associated with these changes is currently being investigated. Experiments are also in progress examining the morphology of non-stimulated axons in ChR2+ rats and in rats subjected only to viral tracing.
MEPs in the non-stimulated hemisphere differed from those in the stimulated hemisphere, suggesting an effect of chronic optical iTBS on physiological responses. ICMS in stimulated M1 produced EMG responses at lower currents and shorter latencies than in homotopic non-stimulated hemisphere.
Using a rigorous method for identifying chronically stimulated and non-stimulated axons, we show that activity causes increased CST axon length and branching, specific to activated neurons. Activity appears to strengthen motor output and expands the M1 motor map. Our study shows that chronic optical iTBS—over a short daily period—restructures CST projections to the spinal cord.

Disclosures: L. Yang: None. **J.H. Martin:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

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Program#/Poster#: 142.08/CC23

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH RO1 NS091031

Title: The cortical origin of extensive corticospinal tract terminal sprouting following cervical spinal cord injury in macaques

Authors: *K. M. FISHER, A. LILAK, C. DARIAN-SMITH
Dept of Comparative Med., Stanford Univ., Stanford, CA

Abstract: Macaque monkeys, like humans, have sophisticated hand function, which is mediated primarily by the corticospinal tract (CST). While most research has focused on the motor (M1) CST, this component of the tract accounts for only 30 % of its total. Another 30% of descending fibers originate in primary somatosensory cortex (S1), and the remaining 40% from many additional cortical sites. Previous work in our lab has shown that sensory and motor CST components respond quite differently to different types of cervical spinal cord lesions. For example, following a combined dorsal root/dorsal column lesion (DRL/DCL) that affects only the first 3 digits of the hand, the M1 and S1 CSTs sprout extensively and bilaterally within the cervical spinal cord, well beyond their normal domain (Darian-Smith et al., 2014). However, the cortical hemispheric origin of this extensive sprouting is not known, since both hemispheres

were injected with the same anterograde tracer in our previous investigations. In the current study we address this directly. Four macaques were lesioned as before, by recording from C5-C8 dorsal rootlets and selectively lesioning those supplying digits 1-3, as well as the cuneate fasciculus of the dorsal column (at the rostral boundary of the rootlet lesion in C5). Recovery from movement deficits was evident after 3 months. At that time, the S1 cortex (contralateral to the lesion), was mapped electrophysiologically, and anterograde tracer injections were made into the digit region of S1 and M1, where reorganization is known to occur. The cervical cord and cortex were sectioned and processed to visualize the anterograde tracers, and a sequential series of sections mapped (NeuroLucida, MicroBrightfield Inc), to determine terminal distribution patterns.
Our findings indicate that for the M1 CST, sprouting originates from both hemispheres, while for the S1 CST, almost 100% of the sprouting originates from cortex contralateral to the lesion. They also indicate that the central immune response contributes bilaterally to the axonal sprouting observed, but not necessarily to functional recovery.

Disclosures: **K.M. Fisher:** None. **A. Lilak:** None. **C. Darian-Smith:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Program#/Poster#: 142.09/CC24

Topic: E.09. Spinal Cord Injury and Plasticity

Title: A small molecule screen identifies novel compounds that re-activate functionally dormant connections within incomplete spinal cord injury circuits

Authors: *N. SALAH[1,2], B. CHEN[1]
[1]Neurobio., Boston Childrens Hospital-Harvard Med. Sch., Boston, MA; [2]Life Sci. and Technologies, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

Abstract: Spinal cord injuries (SCI) tend to result in loss of locomotor function below the injury site in patients. So far, apart from rehabilitative training yielding in suboptimal recovery, the lack of reliable treatment for such patients remains apparent. To investigate this, a staggered lesion was performed over thoracic levels T7 and T10 of the spinal cord which completely deprived descending supraspinal axons to reach lumbar motor neurons that control hindlimb muscles, but spared an inter-lesion zone which provides room for commissural propriospinal axons to act as a link between lesions. We also used a full transection model as a negative control where all supraspinal and propriospinal axons were severed at the lesion site. We reasoned that an important factor in impacting the functional integration of spared axons is the receptiveness of the local spinal circuits. It has been reported that altering excitability by applying epidural stimulation in the spinal cord could promote functional recovery, however, there has been

controversial views whether inhibiting or enhancing the excitability of local neurons is beneficial to functional recovery after SCI. Considering the numerous neural subtypes in the spinal cord, targeting through a genetic-based approach will be difficult to survey possible mechanisms; in contrast, a number of small molecule compounds have been developed to target a variety of neuronal proteins that regulate neuronal excitability. Therefore, we are taking a small molecule screening approach to seek for ones that can activate such functionally dormant connections to mediate functional recovery. In addition, the drug therapy is coupled with a simple yet effective rehabilitative training paradigm that utilizes the concept of water wading to aid with body weight support. The training lasts for 8 weeks, initially with a high level of support (which directly correlates with the water level the mice are placed in) then gradually decreasing the support over the course of the therapy. It is our hope that we will be able to achieve significant functional recovery as evidenced by the Basso Mouse Scale (BMS) score and detailed kinematics analysis during voluntary locomotion following the course of our treatment.

Disclosures: N. Salah: None. **B. Chen:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: CH Neilsen 295319

Title: Enteral pharmaconutrient effects on intestinal epithelial function following acute experimental spinal cord injury

Authors: *G. M. HOLMES, A. R. WHITE, E. N. BLANKE
Neural & Behavioral Sci., Penn State Univ. Col. of Med., Hershey, PA

Abstract: Supplemental enteral nutrition confers improved outcome in the care of critically injured patients. The pharmaconutrients glutamine and arginine are hypothesized to protect enteral health, in part, through the augmentation of local vascular and nutrient homeostasis. The application of clinical nutrition tailored specifically for individuals with spinal cord injury (SCI) remains controversial and poorly defined and the efficacy of pharmaconutrients for sustaining GI barrier integrity and active ion transport following T3-SCI remain obscure. Male Wistar rats received a 300kdyn T3-SCI or surgical control. Three days post-injury, both groups were re-anesthetized and underwent an *in-vivo* intestinal loop preparation. The jejunum was divided into an isolated 10-cm loop by occluding the lumen with 3-0 silk ligatures and filling the loop with 10mM or 100mM concentration of arginine, glutamine or the non-absorbable control substrate, mannitol. An equal portion of proximal jejunum served as an untreated internal control. After 2-

hours, animals were euthanized; jejunal intestinal explants were mounted in Ussing chambers; and epithelial function was measured for transepithelial resistance (TER, a measure of barrier integrity and passive ion transport) and short circuit current (Isc, a measure of active ion transport). At the low (10mM) doses, there were no significant within group differences in TER comparing exposed tissue to unexposed tissue for any pharmaconutrient group. Between surgical treatment group comparisons were also not significantly different. While there were no significant between group differences in initial Isc values comparing exposed tissue to unexposed tissue for any pharmaconutrient group, the tissue from the 10mM arginine exposed loop did display a significant attenuation in longevity of the preparation. Between surgical treatment group comparisons were also not significantly different. Rats administered 100mM arginine demonstrated a substantial (ca. 35%) reduction in viable tissue samples from the unexposed tissue of T3-SCI rats. We were unable to determine of the higher percentage of surviving tissue was a result of the exposure to 100mM arginine or simply a reflection of the unexposed tissue being rostral to the jejunal loop. Our data suggest that T3-SCI does not provoke a significant alteration in passive ion transport (TER) or active ion transport (Isc) of the jejunum. Administering glutamine or arginine did not reliably confer any protective effect upon jejunal luminal epithelium. The effect of pharmaconutrient supplementation upon enteric ganglia function and smooth muscle contractions remains to be determined.

Disclosures: G.M. Holmes: None. **A.R. White:** None. **E.N. Blanke:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 142.11/CC26

Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH R01 R01NS064004

Title: Leveraging activity and guidance to promote sprouting of direct connections between corticospinal tract axons and spinal motoneurons in PlexinA1^{ff} mice

Authors: *J. KALAMBOGIAS[1,2], Z. GU[3], Y. YOSHIDA[3], J. H. MARTIN[2], S. LAU[2], A. SHAMULZAI[4], A. JAMMAL[4]
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Abstract: The corticospinal tract (CST) is critical for skilled voluntary movements. In many monkey species and humans, the CST makes connections both onto interneurons and motoneurons. In rodents, CST connections are made primarily with spinal cord interneurons.

Direct corticomotoneuronal (CM) connections in monkeys, which originate primarily from motor cortex (M1), are associated with improved hand dexterity. Mice with conditional forebrain deletion of the gene for PlexinA1 have an abundance of CM connections, based on confocal microscopy and stimulus-triggered averaging (StTA) from M1 and from the CST in the dorsal column (Gu et al, submitted, Kalambogias et al; SFN abstracts 2014, 2016). This effect of gene deletion is attributable to eliminating axon repulsion and maintenance of exuberant projections during development due to loss of CST PlexinA1-Semaphorin6D signaling. Here we use a novel dual strategy to promote CM connections in mature mice. First, we use virally-mediated PlexA1 gene ablation in $PlxA1^{ff}$ controls by AAV-Cre injections into M1. Second, we use a neural activation protocol that, based on our previous and ongoing experiments in rat and mouse, promotes CST sprouting by upregulating an axonal growth program in CST neurons. We hypothesized that by combining the viral and stimulation approaches we would be able to direct the establishment of sprouted connections from the CST to motoneurons in mature mice. AAV-Cre was injected within the M1 forepaw representation of $PlxA1^{ff}$ mice. We stimulated M1 unilaterally for 10 days using implanted epidural electrodes (6 hours/day; Brus-Ramer et al 2007). We assayed for CM connections using M1 StTA and super-resolution confocal microscopy. Following this dual strategy in mature $PlxA1^{ff}$ mice, there were significant increases in CST presynaptic boutons (co-labeled with VGlut1) on individual motoneurons within the distal muscle motor pool compared to controls. AAV-Cre stimulated animals, with more CM connections than controls, have significantly shorter StTA onset latencies compared with controls, consistent with more direct CST projections from M1. Quantification of the number and topography of CST presynaptic boutons on motoneurons using unbiased stereological assessment are in progress. Our findings show that combined chronic M1 stimulation and PlxA1 gene ablation in mature mice promotes activity-dependent sprouting and targeted outgrowth of CST axons onto forelimb motoneurons directly. By combining neuromodulatory and genetic approaches to establish CM connections we hope to develop a novel approach for promoting recovery of motor function after spinal cord injury.

Disclosures: J. Kalambogias: None. **Z. Gu:** None. **Y. Yoshida:** None. **J.H. Martin:** None. **S. Lau:** None. **A. Shamulzai:** None. **A. Jammal:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 142.12/CC27

Topic: E.09. Spinal Cord Injury and Plasticity

Support: Wellcome Trust Senior Fellowship Grant 106149

Title: Boosting corticospinal transmission to upper-limb muscles with cervical spinal stimulation

Authors: *A. JACKSON, J. KERSEY, C. TERRY, M. BAKER
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Abstract: An emerging application of spinal cord stimulation after neurological injury is to raise the excitability of motorneurons and thus unmask weakened descending projections from the brain. To optimise the targets and patterns of stimulation for maximal facilitation of upper-limb movements, we conducted a series of experiments in anaesthetised, neurologically intact macaques. Weak inputs to the spinal cord were simulated by intracortical microstimulation (ICMS) of the hand area of primary motor cortex, while electromyogram responses were recorded from a variety of upper-limb muscles. We tested facilitatory effects of single pulses and trains (10 to 200 Hz) of subthreshold cervical spinal cord stimulation using ventral epidural, dorsal epidural and dorsal transcutaneous electrodes. In addition, we characterised the motor output elicited by suprathreshold spinal stimulation alone. Suprathreshold stimulation of the ventral cord elicited robust motor responses that reliably followed even high-frequency stimulation trains while motor responses to dorsal spinal cord stimulation exhibited both short-interval facilitation and longer-interval suppression. Due to the slow time-course of the suppression decay (~100 ms), the response to later pulses in high-frequency stimulation trains was gradually abolished. Single pulses of spinal cord stimulation delivered to dorsal but not ventral epidural sites boosted ICMS responses with inter-stimulus intervals of up to 20 ms. Similar results were obtained using transcutaneous stimulation. The facilitation resulting from trains of stimulation was frequency-dependent with an optimal frequency of 20-50 Hz. Higher frequencies produced a diminishing facilitation that mirrored responses to suprathreshold stimulation alone. However, no net suppression of the ICMS response was observed. These results could be explained by a simple model in which spinal cord stimulation generated transsynaptic inputs to motorneurons, and also suppressed subsequent spinal (but not cortical) inputs. We conclude that subthreshold stimulation of the dorsal side of the spinal cord by epidural or transcutaneous stimulation increases the excitability of motorneurons through synaptic input from afferent pathways. However, presynaptic inhibition reduces the efficacy of high-frequency trains of stimulation. We suggest that patterned stimulation may thus be more effective than constant interval stimulation. Moreover, the facilitation of cortically-evoked motor responses may provide a useful measure for optimising stimulation patterns on a patient-specific basis.

Disclosures: **A. Jackson:** None. **J. Kersey:** None. **C. Terry:** None. **M. Baker:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

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Program#/Poster#: 142.13/CC28

Topic: E.09. Spinal Cord Injury and Plasticity

Support: International Spinal Research Trust

Wings for Life

Craig H. Neilsen Foundation

Dept. of Pediatrics, Case Western Reserve University, Rainbow Babies & Children's Hospital

Title: Rapid and robust recovery of breathing 1.5 years after cervical spinal cord injury

Authors: *P. M. WARREN[1,2], S. C. STEIGER[3], T. E. DICK[4], P. M. MACFARLANE[5], W. J. ALILAIN[6,2], J. SILVER[2]
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Abstract: Methods to restore respiratory function following chronic cervical spinal cord injury (SCI) have not been extensively studied. This represents a major gap in our current understanding as the primary cause of morbidity and mortality following cervical SCI is respiratory motor dysfunction. The loss of this activity after SCI is caused by disruption to supraspinal control of motor pathways. We have previously shown that formation of the chondroitin sulphate proteoglycan (CSPG) rich perineuronal net is the major impediment to sprouting and reawakening of the residual cross-phrenic pathway that can lead to restoration of respiratory motor function. Indeed, our data demonstrate that robust and rapid recovery of respiratory motor function is possible up to 1.5 years following severe cervical spinal cord hemisection injury through a combination of enzymatic degradation of perineuronal net associated proteoglycans and rehabilitative conditioning. We now provide evidence that this recovery is essentially permanent, lasting up to six months following the cessation of treatment. Our combination treatment strategy mitigates these effects through CSPG breakdown by intraspinal injection of chrondroitinase ABC (ChABC) and intermittent hypoxia (IH) training to increase respiratory drive and synaptic strength. Following conclusion of our treatment strategy, immunohistochemistry has revealed that the extracellular matrix does not reform normally, perhaps suggestive of on-going plasticity. Further, we provide evidence that our combination treatment strategy allows for re-innervation of diaphragm neuromuscular junctions (NMJs) previously denervated due to paralysis induced atrophy. In addition, we provide data describing the ventilatory response of our animals throughout treatment detailing how our recovered animals respond to environmental challenge. Collectively, these data demonstrate the significant restoration of diaphragm function and nerve activity at chronic points following cervical SCI due to matrix modification, induction of plasticity and facilitation of drive. Indeed, our results indicate that essentially complete recovery of motor function in this model of spinal cord trauma may not be limited by time after injury.

Disclosures: P.M. Warren: None. **S.C. Steiger:** None. **T.E. Dick:** None. **P.M. MacFarlane:** None. **W.J. Alilain:** None. **J. Silver:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Dr. Miriam and Sheldon G. Adelson Medical Foundation

Wings for Life

Title: Multi-cellular foreign body response determines the efficacy and duration of drug delivery from hydrogels in the central nervous system

Authors: *T. M. O'SHEA[1], A. L. WOLLENBERG[2], A. M. BERNSTEIN[1], Y. AO[1], T. DEMING[2], M. V. SOFRONIEW[1]
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Abstract: Injectable biomaterials have the potential to provide prolonged local delivery of drugs to the central nervous system (CNS) for treatment of various neurological diseases. However, investigations employing biomaterial carriers within preclinical models of CNS injury and disease have shown inconsistent and sub-optimal performance. Solving these problems may benefit from a better understanding of (i) the biomaterial and drug parameters that influence the spatial tissue distribution and temporal release characteristics of delivered drugs, and (ii) the multicellular foreign body response to biomaterials that is unique to the CNS. To undertake a rigorous study of biomaterial based drug delivery in the CNS, we developed a tunable molecular delivery system comprising an ethoxylated polyol (EP) based microgel platform that can be readily suspended within a variety of standard physically crosslinked hydrogel materials. Using this composite EP microgel-physical hydrogel system we characterized the spatial and temporal release profiles of various hydrophilic macromolecules and hydrophobic small molecules *in vitro* and *in vivo* within the healthy and traumatically injured CNS. By employing fluorescently labeled molecules and transgenic reporter mouse models we demonstrated spatial, temporal and cell specific differences in molecule delivery *in vivo* in the healthy CNS from various commonly used biomaterial formulations. While drug delivery tunability was apparent acutely using the composite biomaterial carriers, prolonged drug release into the CNS parenchyma was significantly and markedly impaired by a multicellular foreign body response that appeared conserved across different biomaterials. To understand how to improve prolonged molecule delivery into the CNS we characterized the important neural and non-neural cellular elements

that are unique to the CNS foreign body response. Disrupting this biomaterial-induced foreign body response using transgenic animals or through complementary local pharmacological intervention, altered drug delivery outcomes.

Disclosures: **T.M. O'Shea:** None. **A.L. Wollenberg:** None. **A.M. Bernstein:** None. **Y. Ao:** None. **T. Deming:** None. **M.V. Sofroniew:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Program#/Poster#: 142.15/CC30

Topic: E.09. Spinal Cord Injury and Plasticity

Support: National Natural Science Foundation of China

Title: Voluntary exercise contributes to behavioral improvement and its potential mechanisms in mice with the genetic absence of the corticospinal tract

Authors: *W. ZHANG, L. ZHOU
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Abstract: Movement deficits in patients with cerebral palsy are still a worldwide problem, which is mainly attributable to the prenatal damage of the corticospinal tract (CST). In precious studies, we established an animal model with the genetic absence of the CST by conditionally inactivating *Celsr3* in corticospinal motor neurons (*Emx1-Cre;Celsr3*$^{f/-}$ mice) and found that spontaneous plasticity of the motor network partially contributed to functional recovery. However, *Emx1-Cre;Celsr3*$^{f/-}$ mice still behave movement abnormalities compared to the littermate control. In this study, we assess whether voluntary exercise fosters functional improvement and its potential mechanisms. We kept adult *Emx1-Cre;Celsr3*$^{f/-}$ mice to take running wheels for 12 weeks (the experimental group) and used littermate *Emx1-Cre;Celsr3*$^{f/-}$ mice without additional exercise as the control group. Behavioral analysis using grip tests, grid tests and food-pellet taking showed a significant improvement of motor function after 8-week exercise in the experimental group compared to the control group. The mice in the experimental group displayed a 16% increase in the number of neuromuscular junctions accompanied with the increment of weight and volume in biceps. In addition, the mice with running exercise showed a significant increase of EDU-positive proliferating cells in C4-C6 spinal segments, which number is 5.2 times of that in the control group. About 90% of these proliferating cells are oligodendrocyte lineage (olig2^{+}). Our findings indicate that the voluntary exercise is beneficial for the behavioral performance and the motor network plasticity, and the oligodendrocyte proliferating maybe involved in this process. This study will provide us the basic knowledge of exercise rehabilitation for the cerebral palsy in clinic.

Keywords: Corticospinal tract; voluntary exercise; skilled movements; Microglia cells; Profliferation

Disclosures: **W. Zhang:** None. **L. Zhou:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 142.16/CC31

Topic: E.09. Spinal Cord Injury and Plasticity

Title: Molecular targets of trans-spinal direct current stimulation (tsdcs)

Authors: S. SAMADDAR[1], S. BEGUM[2], P. TORUNO[2], M. SALEH[2], W. MEKHAEL[2], *Z. AHMED[2]
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Abstract: Trans-spinal direct current stimulation (tsDCS) is a non-invasive powerful tool demonstrated to positively affect behavior and motor function. tsDCS is a neuromodulatory technique capable of altering spinal and cortical excitability and even regain motor function after complete motor paralysis (Cortes et at, 2017). tsDCS causes immediate and long-term effects in spinal excitability (Ahmed, 2011, 2013; Ahmed and Wieraszko, 2012; Cogiamanian et al., 2011, 2012). Studies have been conducted on both healthy and injured subjects. The ultimate goal is to ameliorate the devastating effects of Spinal Cord Injury. Though researchers have been successful in improving motor function, the molecular basis of the recovery still remains unknown. Our objective for this study was to investigate the effect of tsDCS on several molecular targets including growth factors and other crucial transporters and signaling molecules on both healthy and injured animals to understand the precise pathways involved in strengthening the motor function and recovery of the tissue after injury. Our study groups include Injured and stimulated animals, only injured animals and only stimulated animals. Stimulation paradigm is includes single session stimulation (30 min, 90 min and 2 hours), repeated stimulation (consecutive stimulation for 7 days). We have analyzed several trophic growth factors like nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF). We have also studied a neuron specific transporter protein known to be downregulated after Spinal Cord Injury (SCI), Potassium Chloride Cotransporter 2 (KCC2) and a neuroprotective protein HSP70 along with several anatomical markers like CD31 and NF200. Our data indicate that, after repeated stimulation, the expression levels of BDNF, TrkB, VEGF, KCC2 and PKCC2 increased during cathodal tsDC stimulation when compared with control, sham and anodal stimulation. In contrast, after 40 minutes, 90 minutes and seven days stimulation, the expression of the NGF upregulated during anodal stimulation when compared with the control, sham and cathodal stimulation. We also

investigated the expression levels of BDNF and HSP-70 after 40 minutes and 90 minutes stimulation, results showed that cathodal simulation was significantly higher than sham and anodal stimulation. These findings will help us understand the pathways involved in regeneration, repair and recovery and will lay the foundation for future therapeutic strategies

Disclosures: **S. Samaddar:** None. **S. Begum:** None. **P. Toruno:** None. **M. Saleh:** None. **W. Mekhael:** None. **Z. Ahmed:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 142.17/CC32

Topic: E.09. Spinal Cord Injury and Plasticity

Support: Brody Family Medical Trust Fund Fellowship in "Incurable diseases" of The Philadelphia Foundation.

Craig H. Neilsen Foundation

Title: Modularity and spinal adaptation in leg-based robot locomotion rehabilitation after complete SCI

Authors: *D. LOGAN[1], S. F. GISZTER[2]
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Abstract: Rehabilitation and epidural stimulation (ES) tests of locomotion after spinal cord injury (SCI) in rodent models have both informed and sometimes guided practice in the clinic. Here we tested a combined approach of Adeno-associated viral delivery of Brain-derived neurotrophic factor (AAV5-BDNF) and dual site ES when applied in an impedance-based robot-driven air stepping rehabilitation setting. We sought to examine transfer of training to robot-assisted treadmill locomotion tests, and we compared function achieved with that obtained from pelvic robot rehabilitation alone. We also investigated the organization of hindlimb muscle function throughout our rehab using modularity analyses. SD rats (n=11) were implanted with hindlimb EMGs (9) prior to complete transection (T10) and also with stimulating electrodes on spinal cord dura at L2 & S1. All rats received AAV5-BDNF microinjections caudal to injury. After recovery, all animals were trained 5x weekly (20 min/session) with an ankle-based robotics system consisting of two robots (OMNI, Sensable/3Dsystems) programmed to drive ankle kinematics with an impedance control interaction. One group of these animals (ES, n=6) received constant 40 Hz ES while the other group (No-ES, n=5) did not. Animals were functionally scored (AOB) after injury prior to training and then weekly during a robotic-assisted (at pelvis) treadmill locomotion task. Weekly 20 min ES with a 40 Hz signal stochastically

modulated was used in all animals to elicit stepping motions for Infomax ICA of muscle activations. ES animals made significantly (ANCOVA, p<.01) larger improvements in functional scores (AOB) throughout the rehabilitation period. However, scores were lower than rats with pelvic robot rehab. Here ES animals produced stepping motions with modules needed to reach 90% VAF increasing from 4.3 to 5.3, on average, from day one of training until day ten. During this same period, the no-ES group showed a decrease in number of modules needed to reach 90% VAF of 4 to 3.4. The number of modules needed to reach 90% VAF came back over training days 20-30 to 4.3 and 4, on average, in the ES and no-ES groups, respectively. The early alterations in modularity reflect spinal adaptation processes which were likely resulting from the interaction of BDNF with ES and with leg-based robot training. These observed modularity may be slightly detrimental to treadmill function in passive ankle-based robotics, compared to ES ankle robot training or pelvic robot training.

Disclosures: D. Logan: None. **S.F. Giszter:** None.

Poster

142. Spinal Cord Injury: Stimulation and Rehabilitation

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: NYS Spinal Cord Injury Research Board contract 31291GG (JM)

Title: Augmenting corticospinal output with patterned motor cortex stimulation (iTBS) alone or combined trans-spinal direct current stimulation (tsDC) in a large animal model

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Abstract: An important strategy for rewiring and strengthening the corticospinal system (CS) following injury is to augment activity-dependent mechanisms that promote adaptive plasticity in the spinal cord. Emerging therapies from our lab use patterned electrical stimulation of motor cortex (M1) alone and in combination with cervical trans-spinal direct current stimulation (tsDCS) in the rat to promote corticospinal axon outgrowth, to strengthen CS connections, and to restore skilled motor function. The overall goal of this study is to translate effective neuromodulatory CS repair therapies from the rat, to a large animal model—cervical spinal cord injury (SCI) in the cat—and ultimately the human. Here, we wished to determine if we could scale the tsDCS stimulation parameters, shown to strongly facilitate MEPs in the rat, and to

translate those findings to the cat. We focused on DC stimulus intensity, stimulus polarity, and tsDCS surface electrode position. To estimate tsDCS current density within the cervical spinal cord, we used FEM modeling. MRI and CT images were obtained postmortem from two cats. The images were co-registered and tissue compartments (including CNS, meninges, CSF, bone, body soft tissues) segmented, and each compartment assigned a conductivity value based on the literature. To evaluate the effects of tsDCS, changes in the M1 motor evoked potential (MEP) in forelimb muscles were recorded before, during and after tsDCS. MEPs were evoked in response to short stimulus trains and an intermittent theta burst stimulation (iTBS) pattern. Preliminary results show that a 20 ms inter-stimulus interval for iTBS is more effective than a 50 ms interval for facilitating MEPs. To achieve maximal DC current within the cervical enlargement, FEM modeling revealed optimal cathode electrode placement over the C2-C8 vertebrae dorsally and the anode on the upper chest ventrally. Results to date confirm our earlier rat findings that cathodal tsDCS is more effective than anodal tsDCS in facilitating MEPs. Stronger tsDCS modulation is achieved with the FEM-optimized electrode positions. Experiments are in progress to evaluate the dual capacity of cathodal tsDCS to facilitate iTBS-evoked changes to maximize CS efficacy. Targeted tsDCS is an effective way to promote the efficacy of M1-evoked muscle activity. We conclude that these translatable neuromodulatory paradigms, informed by FEM modeling, are promising therapies to promote CS drive in humans after weakness following injury, such as stroke or SCI.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 143.01/DD1

Topic: C.09. Brain Injury and Trauma

Support: Wings for Life

Title: Role and expression of CCL3 and its receptors after spinal cord injury

Authors: *A. KRONER-MILSCH
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Abstract: Spinal cord injury (SCI) is a very severe condition which has far-reaching effects on health and quality of life. While the primary tissue damage after SCI occurs from the trauma itself, secondary damage is caused by subsequent events which include hemorrhage and inflammation. This secondary reaction contributes significantly to the pathology and thereby to the severity and extent of the functional deficits. The inflammation after SCI is exacerbated and

prolonged. Modulation of the inflammatory response after SCI might minimize tissue damage and promote an environment that is more permissive for healing and repair. The pro-inflammatory chemokine CCL3 plays an important role in various pathological conditions of the nervous system by initiating and maintaining the pro-inflammatory response. CCL3 has been shown to negatively affect neuropathic pain, autoimmune neuropathy and Multiple Sclerosis and its model Experimental Autoimmune Encephalomyelitis. This project is aimed at investigating and dissecting the roles of CCL3 and its receptors after moderate spinal cord contusion SCI in C57BL/6 mice. Preliminary results suggest that CCL3 mRNA is upregulated early and peaks at 6 hours after SCI. It stays elevated for at least 14 days after injury. The main receptor for CCL3, CCR1, is also upregulated after SCI, as is another receptor (CCR5). CCR4, in contrast, is not changed in response to SCI. Other results suggest that CCL3 knockout mice show improved functional recovery compared to wild type mice, using the BMS score for locomotor recovery. Ongoing and future experiments will confirm expression patterns and behavioral results and assess the impact of CCL3 neutralization after SCI. Our preliminary data suggest a potential role of CCL3 in SCI.

Disclosures: A. Kroner-Milsch: None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Program#/Poster#: 143.02/DD2

Topic: C.09. Brain Injury and Trauma

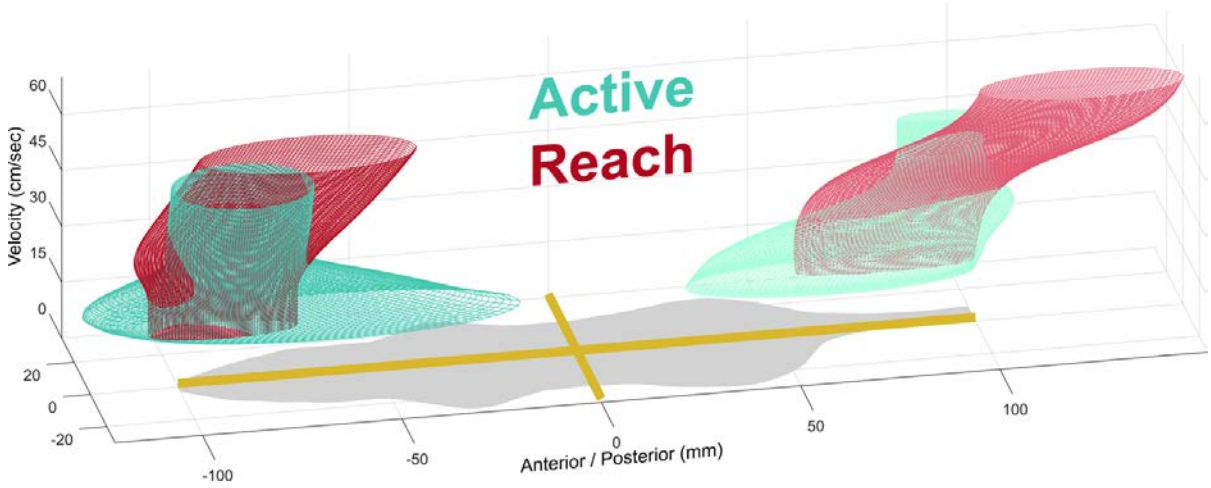
Support: NIH Grant R00HD067339

Title: Gains from robotic gait training are reduced with the addition of skilled forelimb training in a rat model of spinal cord injury

Authors: *N. D. NECKEL
Dept of Neurosci., Georgetown Univ., Washington, DC

Abstract: C4/5 right over-hemisection injuries induce asymmetrical deficits in rats - the right side is more impaired than the left, and the forelimbs are more impaired than the hindlimbs. However, one week after injury rats are able to transverse the CatWalk, albeit with profound locomotor impairments. Spontaneous recovery occurs over time with the more impaired limbs reducing their deficits while the less impaired limbs adopt compensatory techniques. Four weeks of robotic assisted gait training (RAGT) is able to significantly modify the recovery of overground locomotion with each style of RAGT producing slightly different outcomes. Training in viscous fields is less effective than standard body weight supported treadmill training (BWSTT). Actively guiding the limbs through a pre-injury pattern is better than BWSTT, and on

par with training in a negative viscosity field. It is believed that RAGT facilitates recovery by stimulating the proprioceptive networks of the limbs in a coordinated walking pattern while the disrupted supraspinal connections are re-established. In incomplete injuries such as this, we believe that the interneuronal networks near the injury site also need to be stimulated to form more robust relays to successfully reroute the supraspinal signals through the spared tissue. We set out to show that RAGT is more effective when it is paired with training at the level of the injury. Following injury the addition of skilled forelimb training actually reduced the gains found with RAGT alone. MRI imaging shows that skilled forelimb training reduces cellular activity (lower MEMRI contrast), and reduces the organization of the axonal tracks at the injury site (lower FA). This work is further evidence of the competition between motor tasks over spared circuitry. And that this competition can span large distances of the spinal cord as well as disparate motor tasks.



Disclosures: **N.D. Neckel:** None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: VA Merit Award, Northport VAMC

Craig Nielsen Foundation

NYS DOH SCIRB

Title: Non-invasive electromagnetic stimulation of neuro-muscular circuitry: translating from animal research to clinic

Authors: *V. L. ARVANIAN[1], H. PETROSYAN[1,2], S. SISTO[2], M. KAUFMAN[1]
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Abstract: Transmission through the descending motor pathways to lumbar motoneurons and then to leg muscles is essential for walking in humans and rats. After contusion spinal cord injury (SCI), fibers at the injury epicenter are lesioned although some fibers remain anatomically intact. Using animal models of SCI, we have demonstrated that propagation of action potentials and transmission even through these survived fibers to individual spinal cord neurons declines. Synaptic inputs at neuro-muscular pathways are known to function in an activity-dependent manner. As a result of lack of innervation, the function of excitatory glutamate receptors at synaptic inputs to interneurons and motoneurons caudal to injury level is attenuated: a portion of functional synaptic receptors may transition into a "silent" stage, i.e. move from "synaptic" to "extra-synaptic " sites or internalize. In an attempt to recover synaptic function in damaged spinal cord, we used non-invasive electro-magnetic stimulation over spinal levels (SEMS) in order to deliver electric excitation and to initiate propagation of action potentials through the survived axons. We found that SEMS, applied with specific parameters, could strengthen transmission in an LTP-like manner and facilitate function of glutamate receptors at motoneuron synaptic inputs following SCI in adult rats. These physiological changes associated with increased immunoreactivity of GluR1 and GluR2/3 glutamate receptors in lumbar neurons. Importantly, SEMS combined with exercise training induced robust facilitation of locomotor function following SCI in rats; these improvements were retained for 4 weeks after completion of the combined intervention. In order to translate results of these animal experiments to clinical application, we have put together two setups for human studies; one at the Northport VAMC and the other at Stony Brook University. At this time, both setups are functional. At the SFN meeting, we will present technical details and information regarding the construction of these setups. At this time, we anticipate the initiation of human studies. During the initial phase, we will measure aspects of nerve-to-muscle conduction elicited by SEMS: we will measure the compound motor action potentials (CMAPs) recorded from leg muscles and evoked by SEMS and compare characteristics of these CMAPs with H-reflex and M-response in healthy and SCI individuals. Our recent animal studies have shown that properties of CMAP evoked by SEMS can be used for evaluation of conduction at spino-muscular circuitry and thus represents a diagnostic tool to measure the severity of SCI and the effectiveness of the treatments.

Disclosures: V.L. Arvanian: None. **H. Petrosyan:** None. **S. Sisto:** None. **M. Kaufman:** None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 143.04/DD4

Topic: C.09. Brain Injury and Trauma

Title: Comparison of the efficacy and safety of enoxaparin and heparin use in neurointensive care patients

Authors: *S. HUANG[1], Y. AL-KHALILI[1], M. BINNING[2], E. VEZNEDAROGLU[2], K. LIEBMAN[2], C. MAXWELL[2]
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Abstract: Patients with cerebrovascular accident, traumatic brain injury, or spinal cord injury are at increased risk for developing deep vein thrombosis (DVT) and pulmonary embolism (PE) due to CNS injury and prolonged immobilization during recovery. Therefore, preventing clot and thromboembolic formation in neurointensive care patients presents a unique challenge to clinicians who must balance the risk of serious adverse outcomes such as DVT and PE against the progression of any intracranial hemorrhage sustained secondary to injury. While there are numerous studies to support the safety and efficacy of initiating thromboembolism pharmacoprophylaxis early in the treatment, decisions of which agent to use - a low molecular weight heparin such as Enoxaparin or Heparin - are often determined by the clinician preference, hospital formularies, and any additional patient contraindications, such as a history of heparin-induced thrombocytopenia (HIT). Previous studies have shown that Enoxaparin in combination with compression stocking was more effective than compression stocking alone to prevent DVT in patients who has undergone elective neurosurgery. Another study shows that there is no advantage in preventing progression of intracranial hemorrhage incidence in patient groups receiving Enoxaparin or not receiving Enoxaparin after brain injury. The Brain Trauma Foundation Guidelines from 2007 only provide level III recommendation that heparin should be used to prevent DVT in combination with compression stocking, but the guidelines also suggest that there is an increased risk of intracranial hemorrhages associated with heparin use. The ideal prophylaxis agent and dose against DVT in neurointensive care patients is sill unclear. To our knowledge, there are no studies to date that have compared differences in efficacy between the two most widely used agents - Enoxaparin and Heparin - for DVT prophylaxis in neurointensive care patients. We aim to analyze data from 100 patients admitted to neurointensive care for stroke, brain and spinal cord injury who will be randomly assigned to receive Enoxaparin or Heparin for DVT prophylaxis. The incidence of hemorrhage or progression of an existing hemorrhagic lesion and the incidence of DVT will be compared. We hope the data from this prospective study may help guide treatment and practices with the use of DVT prophylactic

agents in neurointensive patients, and potentially demonstrate superiority of one of the two agents examined.

Disclosures: S. Huang: None. **Y. Al-Khalili:** None. **M. Binning:** None. **E. Veznedaroglu:** None. **K. Liebman:** None. **C. Maxwell:** None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 143.05/DD5

Topic: C.09. Brain Injury and Trauma

Support: CONACyT Grand 788

Title: Kynurenine pathway metabolites during the acute and chronic phases of injury in a spinal cord injury model in rats

Authors: *F. C. ESTRELLA, D. RAMIREZ ORTEGA, V. PEREZ DE LA CRUZ, C. RIOS, A. DIAZ RUIZ
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Abstract: Spinal cord injury (SCI) is a public human health issue leading to disabilities and mortality. An incomplete understanding of the physiopathology of the injury has contributed to the development of limited therapies with adverse effects to the patients. One of the mechanisms that has been associated to the enhancement of damage to the spinal cord is the inflammatory response. The inflammation activates several metabolic pathways, including the kynurenine pathway (KP). KP is the major degradation route for tryptophan (Trp) to produce nicotinamide adenine dinucleotide (NAD^+) mainly. KP also produces intermediate metabolites with either neurotoxic or neuroprotective effects. The increased concentrations of quinolinic acid (QUIN), a toxic agonist of the N-methyl D-aspartate receptor, have been reported during the SCI and therapies proposed for SCI, as methylprednisolone, did not diminished its concentration. Recently, it has been described an increase of K-Kyn in SCI patients that developed depression. Moreover, L-kyn concentrations has been found associated to inflammatory markers, directing Trp to the KP to instead of serotonin synthesis. To date, changes of the KP during the acute or the chronic phase of SCI have not been described. The aim of this study was to quantify the concentration of some of the neuromodulatory metabolites of the KP (Trp, QUIN and kynurenic acid (KYNA)). We used a contusion model of SCI in rats in two phases: acute (2, 4, 6, 24 h) and chronic phase (1 and 2 months) after injury. The quantification of the metabolites was performed in spinal cord tissue by HPLC. We observed an increased concentration of Trp in the animals with the lesion compared with those with only laminectomy in all groups. Regarding to QUIN, we observed a continuous increased of this metabolite up to 24 h, but during the chronic phase

this metabolite showed a slight decrease. KYNA levels decreased in the acute phase but increased in chronic phase. In summary, our results suggest a dynamic change between the different metabolites of the KP. CONACyT Grand 788.

Disclosures: **F.C. Estrella:** None. **D. Ramirez ortega:** None. **V. Perez de la cruz:** None. **C. Rios:** None. **A. Diaz ruiz:** None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Topic: C.09. Brain Injury and Trauma

Support: Department of Defense (DoD) Spinal Cord Injury Research Program (SCIRP) Grant

Title: Spinal cord injured mice develop a long-lasting aversive memory of at-level tactile stimulation

Authors: *D. J. NOBLE, R. DONGMO, S. M. GARRAWAY
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Abstract: Pain, which can be experienced above, at, and below the level of injury, is a clinically relevant outcome of spinal cord injury (SCI). Recently our lab has focused on developing novel assessments of at-level allodynia using rodent models of SCI. We previously observed that 1 week after injury mechanical brush stimulation to the trunk causes an acute increase in respiratory rate (RR) in adult SCI mice, suggesting that at-level pain could be modulated by acute autonomic dysfunction following SCI. Here, we sought to establish a more complete profile of the physio-behavioral changes following injury and their relation to the development and expression of at-level mechanical hypersensitivity. Studies were undertaken in adult C57BL/6 mice with a T10 contusion SCI (70 kdynes, IH impactor) or sham surgery. Using a modified light-dark chamber conditioned place aversion paradigm, we assessed side preferences (% time spent in each compartment) and side-to-side crosses before and at time points ranging from 1 day to 5 weeks after surgery. Starting 1 week after surgery, the mice were given truncal stimulation with a small brush at approximately the level of injury (once/min for 5 mins, at ~ 1 cm/s) while confined to the dark chamber. Preferences and crosses were also monitored during the 10-min periods immediately preceding (pre-stimulation) and following (post-stimulation) stimulation, during which the mice could freely access both chambers. Equivalent 10-min time points were scored before and 1 day following surgery but without any stimulation in the intervening 5 mins. SCI mice showed a selective increase in preference for the light “escape” chamber during the pre-stimulation period at later vs. earlier weeks. The change in preference was first observed 1 week after the initial stimulation, developed gradually, and reached

significance by 4 weeks after injury ($p < 0.05$), consistent with the typical timeline of chronic at-level allodynia. SCI mice also displayed a trend toward increased crosses during later weeks as they recovered from injury. There were no changes in either outcome measure in sham mice over the 5-week testing period. Surprisingly, both groups responded similarly to the stimulation on a more acute timescale, with indistinguishable post-stimulation preferences across the 5 weeks. We conclude that mice develop a long-lasting memory of manually applied brush stimulation following SCI that reflects the transition of mechanical stimulation from innocuous to aversive. Together with early autonomic dysfunction, long-term avoidance of repeated stimulation of the trunk may serve as a marker for the development of at-level mechanical allodynia.

Disclosures: D.J. Noble: None. **R. Dongmo:** None. **S.M. Garraway:** None.

Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: C.09. Brain Injury and Trauma

Support: FNS grant NeuGrasp [205321_170032]

Wyss Center for Bio and Neuroengineering

Bertarelli Foundation

Title: Development of an intraneural peripheral stimulation paradigm for reversing hand paralysis in non-human primates

Authors: *M. BADI[1], S. WURTH[1], M. KAESER[2], M. CAPOGROSSO[2], S. DURAND[3], W. RAFFOUL[3], G. COURTINE[4], E. ROUILLER[2], S. MICERA[1]
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Abstract: Regaining the capacity to grasp and manipulate objects is of crucial importance to people living with upper limb paralysis. Functional electrical stimulation of forearm muscles has been used to reanimate paralyzed muscles. However, complex setups requiring multiple muscles to be independently implanted and simultaneously controlled have so far hindered the functional restoration of hand and wrist movements beyond predetermined grasp types. Intraneural peripheral interfaces that present high spatial selectivity in the recruitment of muscles represent an alternative solution to overcome these limitations. Here we present the first steps towards the development of a neuroprosthesis based on intraneural stimulation for the restoration of precise hand movements in a non-human primate (NHP) model of transient paralysis. We investigated

the fascicular topography and the branching patterns of the three main nerves involved in grasping (ulnar, median and radial nerves) to determine the optimal anatomical location of the intraneural interface. Using this morphological data, we built an anatomically realistic computational model of the nerves and their interactions with electrical stimulation. Simulations guided the design of an intraneural implant targeting the different fascicules of each nerve in order to maximize the selective recruitment of hand muscles. We are currently validating the functional properties of these intraneural electrodes experimentally. Our objective is to develop stimulation paradigms that evoke a repertoire of grasping movements in transitorily paralyzed NHP.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: C.09. Brain Injury and Trauma

Support: Verticale, patient organization

Demain debout Aquitaine, patient organization

Labex NUMEV, Montpellier

Title: Longitudinal ^{1}H-MRI analysis and histological characterisation after spinal cord injury in two mouse strains with different functional recovery

Authors: *G. P. SAINT-MARTIN, H. N. NORISTANI, M. CARDOSO, M. CATTEAU, C. COILLOT, C. GOZE-BAC, F. E. PERRIN
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Abstract: Spinal cord injuries (SCI) are devastating neuropathologies that yield to major handicaps from minimal sensory deficits to complete tetraplegia. Currently, there is no effective treatment. Magnetic resonance imaging (MRI) is a non-invasive method widely used to diagnose and follow patients with spinal cord injury. Considering the possibility to perform longitudinal assessment, MRI has great potential for clinical translation. The purpose of our study was to use MRI to assess if the differential recovery observed in two commonly used strain of mice ($CX3CR1^{+/GFP}$ and Aldh1l1-EGFP) after SCI is reflected by distinctive MRI signals. First, we demonstrated that $CX3CR1^{+/GFP}$ mice showed a better functional recovery after SCI compared to Aldh1l1-EGFP mice. Indeed, we observed a better weight support of the hind limbs and a better inter-paw coordination. Moreover, this was associated with a reduced post-injury stress, a better

bodyweight gain and a preserved gross sensory response. Second, we observed similar evolution of the lesion in both CX3CR1+/GFP and Aldh1l1-EGFP mice using *in* and *ex vivo* ^{1}H-MRI. Third, toluidine blue staining confirmed similar lesion size in the two strain of mice; thus demonstrating a correlation between longitudinal *in* and *ex vivo* ^{1}H-MRI and histological analyses. Forth, we carried out immunostaining to assess glial reactivity. CX3CR1$^{+/GFP}$ mice showed reduced microglia and astrocytes immunoreactivity. Finally, we examined serotonergic innervation using serotonin-transporter (SERT) antibody and described a higher density of SERT positive axons in CX3CR1 $^{+/GFP}$ mice as compared to Aldh1l1-EGFP. In conclusion, behavioral improvement did not correlate with modification of MRI signals. However, longitudinal *in vivo* and *ex vivo* ^{1}H-MRI as well as histology showed similar assessments of the lesion size (extension and volume). These findings suggest that *in vivo* ^{1}H-MRI is a reliable technique to examine lesion evolution in mouse models of SCI and could be further used to evaluate therapeutic strategies on SCI.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: C.09. Brain Injury and Trauma

Support: Verticale, Patient Organization

Demain Debout Aquitaine, Patient Organization

Labex NUMEV, Montpellier

Title: A novel translational modl of spinal cord injury in non-human primate : From behavior to magnetic resonance imaging

Authors: *F. E. PERRIN[1], H. N. NORISTANI[2], M. LE CORRE[3], N. MESTRE-FRANCES[2], G. P. SAINT-MARTIN[4], C. COILLOT[5], C. GOZE-BAC[5], N. LONJON[2]
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Abstract: Spinal cord injuries (SCI) lead to major handicaps affecting over 2.5 million people worldwide. Major shortcomings in therapeutic translation to clinics is due to many factors including species differences, development of predictive animal models and differences in tools

used between research and the clinics.
To overcome these obstacles, we first conducted a comparative neuroanatomical analysis of the spinal cord between mouse, *Microcebus murinus,* a non-human primate and human. The general organization and glial cell distribution/morphology in *Microcebus murinus* closely resembles that of human spinal cord. Secondly, we developed and characterized a new model of lateral spinal cord hemisection in *Microcebus murinus* and carried out detailed behavioral and *in vivo* magnetic resonance imaging (^{1}H-MRI) longitudinal monitoring of the animals over 3 months after SCI. Animals presented specific motor deficits and spinal cord tissue alterations assessed at different stages after lesion. Thirdly, we correlated data from *in vivo* ^{1}H-MRI, *ex vivo* ^{1}H-MRI and histology regarding the lesion extension and glial reactivity. We found that microglial reactivity coincides with MRI signals after injury. Hemisected *Microcebus murinus* provides a reliable non-human primate model that can be used to promote translation research on SCI and represent an interesting alternative to larger primates.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: C.09. Brain Injury and Trauma

Support: Swiss National Science Foundation Ambizione Program

University of Fribourg

Swiss National Science Foundation NCCR Robotics

Title: Design of electrical stimulation protocol based on spatiotemporal activation of cervical spinal segments during a reaching and grasping task in primates

Authors: *B. BARRA[1], C. ROUX[1], N. GREINER[1,2], E. M. ROUILLER[1], E. SCHMIDLIN[1], M. CAPOGROSSO[1]
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Abstract: Recovery of reaching and grasping ability is a crucial function to recover from cervical spinal cord injury (SCI). Epidural electrical stimulation (EES) has shown promising results in improving limbs motor control after SCI in various animal models and in humans. In particular, spatiotemporal alternation of stimulation bursts during movement restored skilled

locomotion in rats and Rhesus monkeys with SCI. By mimicking spinal segments activation patterns, these refined stimulation protocols could be pivotal also for the recovery of functional reaching and grasping movements. Indeed, skilled arm control requires complex coordinated activations of multiple arm/hand muscles that might be difficult to achieve with simple continuous stimulation protocols. Here we studied the activation patterns of motor-pools in the cervical spinal cord during a reaching and grasping task in primates, for the design of spatiotemporal cervical epidural stimulation protocols. Intramuscular electromyographic (EMG) activity was recorded from eight muscles of a Macaca fascicularis monkey during the repeated execution of a drawer-opening task involving reaching and grasping movements. Sessions were repeated daily and at various drawer friction levels. We automatically extracted intra-movement phases to differentiate between limb flexion, limb extension and grasp phases. Relying on an established motoneuronal map, we projected muscle activity to the corresponding cervical spinal cord segments to extract the spinal cord spatiotemporal activation maps for each of these phases. The spatiotemporal map highlighted well defined spatially and temporally specific motoneuronal activations. While changes in the force required for the drawer opening were reflected into intensity variations in the spinal activation maps, the overall activation pattern was preserved. Moreover, the spinal maps were reproducible across sessions performed on different days. Based on these insights we propose a simple spatiotemporal stimulation protocol mimicking the natural synergistic muscle activation during upper limb movements. In conclusion, we showed that is possible to define simple task specific spatiotemporal neuromodulation protocols for inducing coordinated activation of multiple arm and hand muscles using epidural stimulation of the cervical spinal cord.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: C.09. Brain Injury and Trauma

Support: CIHR; MOP-142288

Title: Chronic inactivation of the contralesional motor cortex after unilateral thoracic spinal cord injury impedes hindlimb motor recovery

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Abstract: After unilateral spinal cord injury (SCI) at thoracic level in the rat, the lower limb on the side of the lesion is initially paralyzed but recovery typically occurs within 3 weeks. Although the motor cortex and descending corticospinal projections in the rat are predominantly crossed, we recently found that at the time of recovery, plasticity in the ipsilesional motor cortex participates in the recovery of the affected hindlimb. Using intracortical microstimulation (ICMS) to derive hindlimb motor maps, we found that the ipsilesional motor cortex developed a transient representation of both hindlimbs 3 weeks after injury. Accordingly, acute inactivation of the ipsilesional motor cortex 3 weeks after injury increased hindlimb foot-faults bilaterally during horizontal ladder crossing. The mechanisms supporting such compensatory plasticity after SCI are unknown. Activity in one cortex is known to influence the contralateral homologous cortex. Further, bilateral movement evoked by cortical stimulation depends on constitutive activity in the contralateral cortex. We therefore tested whether residual activity in the de-efferented contralesional motor cortex after unilateral SCI (T8 hemisection) affects cortical plasticity in the ipsilesional motor cortex and recovery of the affected hindlimb. Female Long-Evans rats were subjected to combined SCI and cannula implantation targeting the contralesional hindlimb motor cortex. Cortical inactivation was achieved with continuous infusion of muscimol (GABA-A agonist, 10mM, 0.11 µL/hr) delivered via osmotic minipumps from the time of injury. Rats with cortical saline infusion served as a SCI control group. Hindlimb motor function was assessed on a horizontal ladder and treadmill prior to and for 3 weeks after SCI In terminal experiments, ICMS was used to derive hindlimb motor maps. Inactivation of the contralesional motor cortex after SCI significantly impeded recovery of the affected hindlimb in both behavioural tasks. Further, cortical inactivation prevented ipsilesional motor map plasticity from gaining control over the affected hindlimb. In conclusion, we propose that residual activity in the contralesional motor cortex during the initial recovery period after unilateral SCI promotes recovery of hindlimb motor function.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Foundation for Physical Therapy Promotion of Doctoral Studies Level II Scholarship

Title: Eccentric-focused downhill training increases myelin along motor tracts after spinal cord injury

Authors: *T. D. FAW[1,2,3], B. LAKHANI[8], L. WORTHEN-CHAUDHARI[4], T. T. THAXTON[3], R. J. DEIBERT[3], L. C. FISHER[3], M. A. BJELAC[5], H. T. NGUYEN[6], P. SCHMALBROCK[6], J. P. SCHMIEDELER[9], D. M. MCTIGUE[7], L. A. BOYD[8], D. BASSO[3]
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Abstract: Activity-dependent myelin plasticity has emerged as a novel mechanism of neuroplasticity with the potential to support functional recovery after central nervous system (CNS) trauma. In fact, animal studies indicate that new myelin formation is required for motor skill learning in the intact CNS. While traditional activity-based rehabilitation paradigms produce modest functional gains after spinal cord injury (SCI), deficits in eccentric motor control persist, making independent ambulation impossible for most individuals. Eccentric-focused, downhill (DH) treadmill training is a novel, challenging intervention that promotes greater skill learning of locomotion in rodent SCI. Therefore, the purpose of these studies was to employ a translational paradigm to determine the extent and mechanism of training-induced myelin plasticity in humans and rodents with SCI. In chronic, incomplete human SCI (n=4), multicomponent T_2 relaxation imaging (MCRI) of the brain and spinal cord occurred at baseline and after a 12-week DH training intervention consisting of four, 5-min bouts of walking on a 10% decline treadmill separated by 5-min seated rest breaks, delivered 3 days/week. Significant increases in myelin water fraction, a histopathologically validated marker of CNS myelination, occurred in premotor and primary motor regions of the brain after DH training ($p<.05$). To determine the mechanisms underlying myelin increases in humans, experiments were performed in two transgenic mouse lines with and without DH training after chronic, severe contusion SCI at T9. *PDGFRα-creER^{T2}:mT/mG* mice allow inducible green fluorescent protein expression in oligodendrocyte progenitor cells (OPC's) to label new myelin produced in untrained or DH trained animals. DH training in mice was performed daily (20 mins/day; 10 min bouts separated by 10 min rest breaks) from 5-7 weeks post injury at 10% decline. Brain and spinal cord MCRI pre/post training was combined with immunohistochemistry to identify training-induced new myelin formation in mice. Genetic deletion of myelin regulatory factor (Myrf) in OPC's prevents their ability to differentiate and form new myelin. Therefore, DH-trained *PDGFRα-creER^{T2}:Myrf$^{(+/-, -/-)}$* mice underwent the same experimental paradigm to determine whether new myelin is required for motor learning of eccentric control after SCI. These preliminary data suggest that eccentric-focused DH training targeting persistent locomotor deficits promotes myelin plasticity in humans with SCI. Ongoing translational experiments in mice will provide valuable insight into the mechanisms underlying this response.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Foundation for Physical Therapy Promotion of Doctoral Studies Level II Scholarship

NIH F31 NS080512

Title: Deficits in eccentric motor control after human and rodent spinal cord injury

Authors: *D. BASSO[1,2], T. D. FAW[1,2,3], M. A. BJELAC[4], T. T. THAXTON[1], R. J. DEIBERT[1], L. C. FISHER[1], M. P. MCNALLY[1], K. J. O'BRIEN[6], A. OLSZEWSKI[6], C. N. HANSEN[2], J. P. SCHMIEDELER[6], L. WORTHEN-CHAUDHARI[5]
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Abstract: Eccentric motor control plays a critical role during locomotion by decelerating the center of mass during weight acceptance, slowing the leg during the swing phase, reducing fatigue, improving efficiency and contributing to other functions. Yet, eccentric locomotor impairments remain largely unexamined in human, rat or murine spinal cord injury (SCI). Here we examine whether eccentric deficits exist and test the impact of task-specific eccentric training on locomotor function across species. In humans and rodents with incomplete SCI, we delivered downslope manually-assisted treadmill training at 10% grade to specifically target eccentric motor control. Downhill (DH) training totaled 20 min/day for all species, with 3 sessions/wk for

12 wks in humans and 9 consecutive sessions in rodents. Training occurred in 5 min (human) or 10 min (rodent) bouts separated by an equal length rest period to prevent delayed onset muscle soreness. Outcome measures included biomechanics and functional tests tailored for each species. In humans, outcome measures were collected during overground locomotion. In rodents, collection occurred in overground and flat treadmill settings. Across species, eccentric deficits included poor or absent weight absorption or yield at ground contact and loss of fractionated joint movements resulting in poor coordination. Eccentric deficits in rat and human SCI also included prolonged semitendinosis activity through early stance or longer, into midstance. During eccentrically controlled descent from standing to sitting, however, semitendinosis activity was absent at more acute joint angles. In all species, DH training improved motor control during functional tasks based on muscle activation, kinetics, performance measures or a combination of those metrics. These findings demonstrate the need to specifically address key motor control deficits during rehabilitation to avoid long-term or permanent functional impairments.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 143.14/DD14

Topic: E.09. Spinal Cord Injury and Plasticity

Support: PVA Research Foundation Grant 3068

NIH SBIR grant R43EB018232

Title: Voluntary modulation of spinally evoked motor potentials in leg muscles after motor complete paralysis

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Abstract: Biofeedback techniques to establish learned voluntary control of specific physiological responses has been effective following different neurological injuries and disorders. After severe spinal cord injury (SCI), however, application of biofeedback is limited due to little to no changes in the resultant motor responses generated by a participant. As such, training and regaining of motor control using conventional techniques are less effective.

We requested three participants with chronic sensory and motor complete SCI, classified as AIS A, and with neurological levels of injury between T2 and T9, to voluntarily modulate motor potentials from the leg muscles, evoked using transcutaneous electrical spinal cord stimulation (tSCS) as a test paradigm, applied to the caudal portion of the lumbosacral enlargement (L1-L2 vertebral level). Single spinal stimuli were delivered while the participants were relaxed in the supine position, and during voluntary efforts to generate knee flexion, knee extension, plantarflexion, and dorsiflexion. The participants observed each evoked potential on a monitor, and were instructed to increase the magnitude of the responses in the given muscle via voluntary effort. The experiment was performed without and with the presence of a second-site tSCS delivered at the rostral portion of the lumbosacral enlargement (T11-T12 vertebral level) at a 30 Hz stimulation frequency, and at sub-motor threshold intensity. Changes in the magnitude of the evoked potentials were calculated bilaterally in the vastus lateralis, medial hamstring, soleus (SOL), and tibialis anterior (TA) muscles.
All subjects were able to voluntarily modulate the evoked potentials in the presence of stimulation. During plantarflexion and dorsiflexion, the magnitude of the motor responses in the SOL and TA increased 13.9±3.0 and 29.6±11.1%, respectively. With the additional second-site tSCS at T11-T12, facilitation significantly increased up to 23.6±10.6 and 309.9±101.1%, respectively.
Our data concur with previous findings demonstrating that epidural spinal cord stimulation can augment voluntary motor control after SCI. We suggest that voluntary modulation of spinally evoked multisegmental potentials in presence of visual biofeedback can be used as a paradigm allowing not only to investigate translesional corticospinal connectivity, but also to train voluntary control after SCI.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: NIH Grant U01EB015521

Title: Combination of epidural stimulation, serotonergic agonist, and rehabilitative training promotes forelimb recovery in cervical spinal cord injured rats

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Abstract: Epidural stimulation (EDS), drug intervention, and motor training are currently some of the most successful treatments to promote functional recovery after a spinal cord injury (SCI). Previously we demonstrated that EDS significantly improved forelimb motor function after a cervical SCI, and later found similar effects with serotonergic agonists. Rehabilitative motor training also has been shown to facilitate functional improvement in animals with an acute or chronic SCI. We have begun to test whether any combination of these treatments may have complementary effects in facilitating forelimb motor recovery, such as grip strength and reaching and grasping, after a cervical injury. Long-Evans rats were trained and then tested on a task involving reach and grasp of a pellet, and on a robotic version of the same task in which the pellet was affixed to a manipulandum. Intramuscular EMG electrodes were implanted in several forelimb muscles and epidural stimulation electrodes were implanted at cervical spinal cord segments C6 and C8. After baseline testing, the rats received a bilateral dorsal funiculi crush injury at spinal cord level C4. Rats were administered buspirone daily (1 mg/kg, ip.), a partial 5-HT_{1A} receptor agonist, and received daily training beginning 1 week post-injury. By 8 weeks post-injury, the success rate for reaching and grasping was greater in EDS/buspirone-treated animals with than without training ($p< 0.01$; two-sample t-test). The number of sMEPs and amplitude of late responses increased with each added treatment, suggesting an increased activation state of the cervical interneuronal motor networks. The improved success rates of reaching and grasping and the changes in sMEPs most likely reflect adapted sensorimotor networks forming a de novo functionally significant supraspinal-spinal connectome. Retrograde labeling transsynaptically via injection of pseudorabies virus 152 into forelimb flexor muscles showed increased sprouting of motor circuitry to the contralateral somatosensory motor cortex of the dominant forelimb in animals treated with buspirone only. Animals that also received rehabilitation with the EDS/buspirone treatment showed a greater increase in the amount of sprouting than in animals without rehabilitation. The results indicate that post-injury treatment with EDS and a serotonin agonist opens a window of opportunity for plasticity that can be guided and further facilitated by motor training.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Christopher & Dana Reeve Foundation

Walkabout Foundation

Title: Enabling descending motor control after spinal cord injury with noisy electrical stimulation delivered by an innovative epidural interface

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Abstract: Spontaneous recoveries after spinal cord injury are extremely rare. Multiple experimental approaches have been considered so far to promote the reconnection of the lesioned spinal cord, but clinical treatments are still missing. Surprisingly, the majority of individuals diagnosed with complete paralysis who have been treated with an experimental protocol of electrical stimulation of the spinal cord have consistently recovered volitional motor control and improved sensory and autonomic functions. The mechanisms responsible for these improvements are still unclear. A working hypothesis is that the diffuse electrical stimulation of spinal networks above, within and below lesion increases spinal network excitability and facilitates weak descending voluntary inputs to recruit lower extremity motor pools (even if electrically incompetent due to spinal cord injury). To ascertain this hypothesis, we applied an innovative protocol of electrical stimulation consisting in the continuous multisegmental delivery, at subthreshold intensity, of two AM/FM biosignals, sampled from a hind limb EMG during walking in a healthy rat, and simultaneously applied with opposite polarity (a protocol named dynamic neuromodulation). Such a complex pattern is applied through a unique epidural stimulating interface composed of 18 fully independent microelectrodes that provide specific activation of distinct motor pools by changing the level and the polarity of each impulse. We have further modeled the resulting distribution of the stimulus waveforms on the various parts of the spinal cord as a function of time by Finite Element Analysis method. In uninjured cords, dynamic neuromodulation facilitates spinal reflexes through sub-threshold electrical single

pulses delivered both along the thoraco-lumbar spinal cord and transcortically to the motor brain areas. The same protocol when acutely applied after a calibrated contusion of the cord restores spinal reflexes and bilateral muscle contractions of the hindlimb.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: B31ieve in Miracles Foundation

Title: Use of FosTRAP mice to analyze and compare spinal motor circuit activation during two different locomotor behaviors

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Abstract: Spinal epidural stimulation (ES) along with pharmacological agents in conjunction with specific physical rehabilitation procedures have enabled treadmill stepping in rats after a complete mid-thoracic spinal cord transection (SCI), and has restored voluntary leg movements in humans with SCI. These improvements in motor function can be seen through behavioral, kinematic, and electrophysiological analysis. However, the plastic changes in the spinal locomotor networks responsible for these recoveries in response to ES and physical rehabilitation remains only partially defined. Previous studies using c-fos to identify neural activation during locomotor tasks before and after SCI could only identify neural activation at a single particular time point and could not compare changes in network activation over time. The FosTRAP mouse model has been developed to allow two different c-fos activation patterns due to two different events to be seen in the same animal. TRAP utilizes tamoxifen-dependent recombinase, $CreER^{T2}$, expressed in an activity-dependent manner which then expresses tdTomato (tdT) in a Cre-dependent manner. This allows genetic access of neural activation during desired time frames which can then be compared to c-fos expressed during a later event. Here we show the

efficacy of FosTRAP mice to identify spinal neurons activated during quadrupedal stepping (QS) in uninjured mice. Optimization experiments for the timing and dosage of 4-hydroxytamoxifen (4-OHT) injections enabled comparisons of neural activation patterns between two different bouts of 30 min QS. Mice received IP injections of 4-OHT at different time points relative to their first bout of 30 minute quadrupedal stepping: 4, 2, and .5 hours before stepping and 1, 2, and 4 hours after stepping. The optimal time point was 30 min before the start of stepping. Dosage experiments of 0, 25, 50, 75, and 100 mg/kg of 4-OHT showed 75 mg/kg as the optimal dose. Optimized dosage and timing injections of 4-OHT showed roughly equal amounts of tdT+ neurons activated during the first bout of QS and cfos+ neurons activated during the second bout of QS. TdT expression in the soma and processes suggested the presence of connections of activated neurons during QS. Application of CLARITY to FosTRAP spinal cords, illustrate the 3-D rostro-caudal and dorso-ventral connections of locomotor networks. Results show similarity in 3D activation patterns due to similar tasks and differences in different locomotor tasks. These methods can greatly facilitate spatial characterization of neuronal types linked to a complex motor task performed *in vivo* and can potentially track network activation changes before and after SCI.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Topic: E.09. Spinal Cord Injury and Plasticity

Support: Russian Foundation for Fundamental Research (Grant No. 16-29-08173-ofi-m)

Title: Imagining stepping as a tool to modulate the physiological state of spinal locomotor networks

Authors: *Y. P. GERASIMENKO[1], J. KOZESNIK[2], P. GAD[3], D. SAYENKO[4], T. MOSHONKINA[6], R. GORODNICHEV[7], A. PUHOV[7], V. EDGERTON[5]
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Abstract: Recently we have demonstrated that multisite non-invasive transcutaneous spinal cord stimulation can facilitate stepping performance in non-injured subjects as well as in SCI patients.

Given the observations that individuals who have been paralyzed for more than a year can regain voluntary control when facilitated with electrical neuromodulatory techniques, we have begun to examine the newly emerged brain-spinal network interactions. In the present study we examined the role of spinal networks in facilitating locomotor movements when the subject was imagining oscillating movements in the presence or absence of multisite transcutaneous spinal cord stimulation. The subjects were asked to imagine bilateral stepping with the eyes closed or visually observing a stick figure stepping on a video monitor and performing rhythmic stepping movements vs when it is stationary. EMG activity of leg muscles and limb kinematics were monitored. Non-invasive spinal cord stimulation was delivered transcutaneously at two independent sites, along the midline between the spinous processes of vertebrae T11–T12, and L1–L2 with frequency of 30 Hz, using a three-channel custom-built constant-current stimulator. Spinally evoked motor responses in leg muscles to L1 stimulation (0.3Hz) as well as to transcranial magnetic stimulation (TMS, (0.1Hz)) were examined. Non-injured subjects (n=17) were tested while lying on their left side with the upper leg supported in a sling directly at the shank and the lower leg placed on a free rotating brace segment attached to a horizontal board supported by vertical ropes secured to hooks in the ceiling. By using this “Zero-G” suspension apparatus, the subject’s legs were supported and allowed to move freely in the sagittal plane in a gravity-neutral manner. When imagining a rhythmic bilateral stepping movement, multisite transcutaneous spinal cord stimulation induced stepping movements at a lower current than when the image was stationary. We have found that during volitional and passive stepping performance as well as during imagining, but not stepping, the spinally evoked motor responses in the leg muscles were inhibited, whereas TMS evoked responses were facilitated. The facilitation of TMS evoked responses during active stepping as well as during imagining was stronger than during passive movements. We suggest that imagining stepping can be a tool to modulate physiological states of spinal networks, thus serve as a functionally dynamic component of the brain-spinal interface to facilitate spinal locomotor networks.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

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Topic: E.09. Spinal Cord Injury and Plasticity

Title: Behavioral and histological changes suggest possible mechanisms underlying the use of epidural stimulation for recovery of voluntary locomotion after incomplete spinal cord injury

Authors: *K. A. DEPETRO, S. ZDUNOWSKI, C. JUAN-SING, R. TRUONG, H. ZHONG, N. TILLAKARATNE, V. R. EDGERTON
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Abstract: We showed previously that epidural stimulation (ES) and step/stand training can restore voluntary control in humans with chronic motor-complete spinal cord injuries (SCI) in as little as 24 hours. However, the mechanism by which this occurs is not yet understood. Theoretically, this improvement could be partially explained by changes in spinal neurons that survive the initial SCI, but become unable to generate action potentials. Voltage- gated sodium channel isoform 1.6 (Nav1.6) is the predominant ion channel required for voluntary movement. Normal clustering at the node of Ranvier is necessary for conduction of the action potential and is facilitated by myelin wraps around the internodal regions in an uninjured state. After SCI, both components are disrupted and associated with further loss of function. The current study investigates whether: 1) motor improvements can occur in the absence of ES after a period of regular step/standing training + ES, and 2) if the node of Ranvier Nav1.6 channels and oligodendrocytes are involved in recovery. Adult female Sprague-Dawley rats (n=12) received either post-injury step/stand training alone (Tr Only Group, n=6) or step/stand training with ES (ES+Tr Group, n=6). Animals were implanted with EMG bilaterally into Tibialis Anterior and Soleus muscles and epidural electrodes at L2/S1 spinal cord segments. All animals received right HX at T8-T9 spinal level and locomotor function was assessed regularly via SIMI-Motion kinematic and EMG analysis. After 29 days post-injury, animals that received ES, compared to those that did not, displayed a higher average step height reported as a percentage of the pre-injury value ($p=.001$; ES+Tr Group: 78.7% ± 2.60%; Tr Only Group: 64.8% ± 3.34%). ES+Tr animals also showed increased trajectory area throughout 10 consecutive steps, indicating improved ability to maintain an elevated foot during swing phase ($p=.03$; ES+Tr Group: 6.95 cm^2 ± 1.73 cm^2; Tr Only Group: 4.36 cm^2 ± 1.59 cm^2). These improvements persisted for at least 24 hours after the last ES session and in the absence of ES during that testing period. Subsequent testing with the epidural stimulator on, at 95% threshold, provided further enhancement (increased step height to 89.6% ± 3.11%). These results indicate that ES may have a more-than-transient effect on spinal networks allowing for marked improvements in locomotor function that persist in the absence of ES. These findings imply significant functional reorganization of spinal networks. Our histological evidence also suggests that changes in oligodendrocytes, the node of Ranvier, and other parameters could have played an important role in defining locomotor function in rats.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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UCLA Clinical and Translational Research Center (CTRC)

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Title: Enabling hand function in chronic spinal cord injury patients with non-invasive transcutaneous stimulation and buspirone: A double-blinded, sham controlled pilot study

Authors: *L. MOORE[1], S. ZDUNOWSKI[1], E. MORIKAWA[1], T. SIERRO[1], D. SAYENKO[1], P. GAD[1], T. HOMSEY[1], M. NUWER[1], D. REINKENSMEYER[2], M. SARRAFZADEH[1], D. MCARTHUR[1], Y. GERASIMENKO[1,3], V. R. EDGERTON[1], D. C. LU[1]
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Abstract: Spinal cord injury (SCI) is one of the leading causes of long term paralysis. For patients with a chronic SCI treatment options are limited. Physical therapy can help maintain general health but little to no functional improvement is expected after the first year of injury. Epidural electrical stimulation of the spinal cord via an implanted epidural electrode array can improve leg function, stabilize posture, and enable volitional movement. Epidural stimulation can result in functional improvement of the hand in quadriplegic patients. In this study, we sought to determine if transcutaneous electrical stimulation of the cervical spinal cord along with oral monoaminergic agonist could result in similar functional improvement of the hand. Twelve subjects were recruited that had been injured for at least a year. Of the recruited subjects, ten of the twelve subjects were motor complete (ASIA score of A or B). It has been reported that training with a handgrip alone did not result in significant improvement in these subjects after chronic testing (Hoffman et al. 2017). For this study, subjects received transcutaneous stimulation alone or in combination with the partial 5HT1A agonist buspirone while training with the handgrip device. Transcutaneous stimulation significantly improved hand function in seven of the twelve enrolled. While buspirone did not improve hand function, in some subjects it reduced spasm severity.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Title: Noninvasive spinal cord stimulation improves arm and hand function after severe paralysis

Authors: *P. GAD[1], S. LEE[2], N. TERRAFRANCA, Jr[3], H. ZHONG[4], A. G. TURNER[5], Y. GERASIMENKO[6], V. EDGERTON[7]
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Abstract: Paralysis of the upper extremities following cervical spinal cord injury (SCI) significantly impairs one's ability to live independently. While regaining hand function or grasping ability is considered to be one of the most desired functions in tetraplegics, minimal significant therapeutic development in this direction has been demonstrated to date in humans. This study demonstrates that noninvasive neuromodulation of the cervical spinal cord, concomitant with training, improved maximum voluntary hand grip forces in both upper limbs by ~17-fold in chronic cervical SCI subjects within eight treatment sessions. The underlying hypothesis is that in SCI subjects the nonfunctional sensory-motor networks within the cervical spinal cord can be transformed to physiological states which dramatically amplifies voluntary control of hand and arm function. The form of transcutaneous spinal cord stimulation as used in the present study, also referred to as painless cutaneous enabling motor control (pcEmc), enabled improved voluntary hand function within a single session of all subjects tested. Biweekly training over the course of eight treatment sessions over 4 weeks in presence of pcEmc increased the average maximum force generated by the left and right hand by 11 and 24-fold, respectively compared to baseline. We demonstrate that, with this novel intervention, the cervical spinal circuitry can be neuromodulated to improve volitional control of hand function in subjects with severe tetraplegia. The improvements in hand function were accompanied by, in some subjects with improvement in autonomic function, lower extremity motor function and sensation below the level of the lesion. Regaining these functions in individuals with severe, chronic upperlimb paralysis had dramatic impacts functionally, psychologically and in their socio-economical state.

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

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Title: Trunk motor control assessment in children with spinal cord injury

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Abstract: Aim: Injury to the spinal cord leads to paralysis, paresis and/or spasticity in trunk musculature, which results in impaired sitting balance and respiration. There is a lack of sensitive outcome measures to assess trunk motor control after pediatric SCI. The aim of this study was evaluate and compare trunk motor function in children with SCI to age-matched typically developing children (TD) by analysis of multi-muscle surface electromyography (sEMG) during assessment of posture and respiration function. The Segmental Assessment of Trunk Control (SATCo) test was incorporated to measure sitting posture control, while respiratory function was examined via spirometry, maximum expiratory (PEmax)& maximum inspiratory (PImax) maneuvers. We hypothesized that trunk motor control is significantly different in children with SCI as measured by sEMG activation patterns compared to TD children. Methods:12 children with cervical or thoracic SCI and 14 TD children (TD) participated. sEMG signals from upper trapezius (UT), pectoralis (PEC), 6th intercostal (INT), rectus abdominus (RA), external oblique (OB) thoracic paraspinal (PS-T) & lumbar paraspinal (PS-L) muscles were recorded during sitting. Outcome measures included root mean square value of sEMG, SATCo scores, spirometry, PEmax and PImax airway pressure. Results: Mean age of children in SCI and TD group was 6±1 and 7±2 years respectively. Children with SCI exhibited lower SATCo score, FVC, FEV1 and PEmax values compared to age-matched TD children. A significant lower ($p<0.05$) activation in trunk muscles (RA, OB & PST) was observed in children with SCI during static trunk control events of SATCo test and PEmax maneuver compared to age-matched TD children. Children with SCI exhibited increased compensatory activation of accessory muscles above the lesion during these tasks. During static sitting task, phasic contraction of PST & PSL muscles was observed in children with SCI, in contrast to the low amplitude tonic activity in TD children. Conclusions: Children with SCI showed trunk motor deficit with low or no activation in RA & OB muscles and phasic activation of PST muscle during these tasks with compensatory activation of muscles (UT & PEC) above the level of lesion. Children with SCI exhibited deficit in both, posture and respiratory function, indicating the multi-functional importance of the trunk musculature. Interestingly, activation of trunk muscles both above and below the anatomical/neurological level of injury (LOI) and across all injury classifications was observed, suggesting that trunk muscle function may not be predicted by the LOI as defined by clinical exam.

Disclosures: G. Singh: None. **S. Trimble:** None. **S. Aslan:** None. **L. Argetsinger:** None. **M. Roberts:** None. **T. Flynn:** None. **A. Ovechkin:** None. **A. Behrman:** 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.; Kosair Charities, Helmsley Charitable Trust, Craig H. Neilsen Foundation, Coulter Translational Research Award. D. Fees for Non-CME Services

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Poster

143. Spinal Cord Injury: Animal Models and Human Studies

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: C.09. Brain Injury and Trauma

Support: National Institute of General Medical Sciences Grant 8 P30 GM-103507

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Title: Assessment of trunk motor function after spinal cord injury

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Abstract: The inability to maintain upright trunk posture without upper extremity support is a primary, debilitating consequence of spinal cord injury (SCI) and paralysis regardless of age at injury. The axial trunk musculature is responsible for the simultaneous maintenance of posture and balance, respiration, and phasic stabilization of the axial spine to allow efficient movement of the extremities [1-3]. Current measurement tools fail to assess activation of the postural musculature after SCI, likely contributing to an underestimation of the importance of the trunk musculature in mobility tasks.
Neurophysiological measures have been developed which incorporate examination of trunk motor function after spinal cord injury. Functional neurophysiological assessment (FNPA) can provide improved sensitivity in the assessment of motor function utilizing multi-muscle surface electromyography recordings to objectively quantify muscle activation patterns during standardized movement attempts [4, 5]. We analyzed trunk muscle activation patterns recording during FNPA assessment of 79 adults with SCI (A=22, B=19), and 9 children (A=6, B=3) with SCI at or above T8.
39/41 adults with motor complete SCI (95.12%) could volitionally activate the erector spinae muscle recorded at the T10 vertebral level. In contrast, rectus abdominus activation was only

observed in 18/41 (27.3%) participants. Similarly, FNPA of children with motor complete SCI also revealed that 9/9 injured at or above T7 could volitionally activate erector spinae at T10, while rectus abdominus activation was observed in 5/9 (56%) participants. Activation of the trunk musculature observed in both assessments was not predicted by AIS motor or sensory scores.
Both clinical and neurophysiological data suggest that the trunk musculature's innervation is complex, and is not predicted by sensory function. As neurorehabilitation shifts away from compensation for movement deficits, and towards strategies promoting functional recovery by means of activity dependent plasticity [6], strategies to engage the trunk musculature will be crucial. Therefore, the standardized, quantitative assessment of trunk control is needed to improve our understanding of the residual networks influencing postural control after SCI, which in turn will aid in the development and evaluation of activities-based therapies targeting improved trunk control after SCI. Historically, there has been no clinical expectation for recovery of the trunk musculature after SCI. The current results suggest that there is significant untapped potential to improve trunk control outcomes after SCI.

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Poster

144. Descending Modulation of Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 144.01/DD24

Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Dysfunction of potassium (SK) channels in the amygdala in a rat model of neuropathic pain

Authors: *J. M. THOMPSON[1], V. A. YAKHNITSA[1], L. MAHIMAINATHAN[1], G. JI[1], V. NEUGEBAUER[1,2]
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuropathic pain is an important healthcare issue with significant emotional-affective components, but underlying maladaptive changes, particularly in the brain, are not well understood. Increased amygdala activity contributes to emotional-affective aspects of pain. Small-conductance calcium-activated potassium (SK) channels are expressed in the amygdala

and can inhibit neuronal excitability through actions that include mediating the medium afterhyperpolarization (mAHP), shunting excitatory synaptic transmission and enhancing inhibitory synaptic transmission. SK channels have been implicated in peripheral and spinal nociceptive processing, but their involvement in pain-related plasticity in the brain has not yet been assessed. Here we test the hypothesis that SK channel dysfunction in the central amygdala (CeA; output nucleus) contributes to neuropathic pain-related maladaptive amygdala plasticity and behaviors. Audible (nocifensive response) and ultrasonic (affective response) vocalizations and mechanical thresholds (von Frey test) were measured in neuropathic rats (L5 spinal nerve ligation model, SNL) and in sham controls 4 weeks after surgery. SNL rats showed increased vocalizations and reduced withdrawal thresholds compared to sham rats. Stereotaxic administration of an SK channel blocker (apamin) into the CeA by microdialysis increased vocalizations in sham but not SNL rats. Patch-clamp recordings of regular firing lateral CeA neurons in brain slices from SNL rats found reduced mAHP, increased action potential frequency-current (F-I) relationship, and enhanced excitatory synaptic transmission compared to sham controls. Apamin blocked the mAHP and increased excitability and excitatory transmission in brain slices from sham but not SNL rats, indicating that SK channel blockade under normal conditions mimics neuropathic pain-related changes, and SK channel activation is lost in the pain state. Western blotting and reverse transcription polymerase chain reaction (RT-PCR) revealed decreased levels of SK2 subunit protein and mRNA in the amygdala of SNL compared to sham rats, suggesting pretranscriptional SK channel downregulation. The data indicate that SK channel dysfunction contributes to maladaptive neuropathic pain-related amygdala plasticity and behavior.

Disclosures: J.M. Thompson: None. **V.A. Yakhnitsa:** None. **L. Mahimainathan:** None. **G. Ji:** None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Optogenetic stimulation of amygdala CRF neurons modulates pain behaviors in an arthritis model

Authors: *K. E. MARSHALL[1], G. JI[1], V. NEUGEBAUER[1,2]
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Abstract: The amygdala is an important neural substrate for the emotional-affective dimension of pain. The central nucleus (CeA) serves major amygdala output functions and receives highly processed nociceptive and affected-related information from the lateral-basolateral network (LA-BLA). The CeA is a major site of extra-hypothalamic expression of corticotropin releasing factor (CRF), and amygdala CRF neurons form widespread projections to target regions involved in behavioral modulation, including brainstem areas to promote aversive and anxiety-like behaviors. The effects of selective modulation of CRF neurons on pain-related behaviors remain to be determined. Here we used optogenetics to activate or silence selectively CRF CeA neurons and BLA projections to the CeA. For optogenetic activation or silencing of BLA axon terminals in the CeA, a viral vector (AAV) encoding channelrhodopsin 2 (ChR2) or enhanced Natronomonas pharaonis halorhodopsin (eNpHR3.0) under the control of the CaMKII promoter was injected stereotaxically into the right BLA. Wireless optical activation of BLA axons in the CeA with blue light pulses (473 nm) delivered through an LED optical fiber in the CeA increased or induced audible and ultrasonic vocalizations under normal conditions. Optical silencing of BLA axons in the CeA with yellow light pulses (590 nm) decreased vocalizations and anxiety-like behavior in the arthritis pain model (kaolin-carrageenan-induced knee joint arthritis). For optogenetic activation and silencing of the CRF neurons in the CeA, a Cre-inducible viral vector (DIO-AAV) encoding ChR2 or eNpHR3.0 under the control of the EF1a promoter was injected stereotaxically into the right CeA of transgenic Crh-Cre rats. Wireless optical activation of CRF CeA neurons with blue light pulses delivered through an LED optical fiber in the CeA increased or induced audible and ultrasonic vocalizations and anxiety-like behavior (OFT) under normal conditions. Optical silencing of CRF CeA neurons with yellow light pulses decreased vocalizations and anxiety-like behavior in the arthritis pain model. The data provide direct evidence for facilitatory effects of BLA-CeA input and of CRF-CeA output under normal conditions and their contribution to pain behaviors in an arthritis model.

Disclosures: K.E. Marshall: None. **G. Ji:** None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Cannabinoid CB1 modulation of basolateral amygdala neuronal activity in a rodent model of arthritis pain revealed by two-photon calcium imaging

Authors: *T. KIRITOSHI[1], V. A. YAKHNITSA[1], V. NEUGEBAUER[1,2]
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Abstract: Pain-related hyperactivity in the basolateral-central amygdala (BLA-CeA) network accounts for emotional and cognitive impairments in pain states. Cannabinoid receptor CB1 can modulate synaptic transmission and pain-related behaviors. CB1 is highly expressed in the BLA but pain-related modulatory effects of CB1 on the population of BLA neurons remain to be determined. In this study, we used two-photon calcium imaging in brain slices to determine the effect of CB1 receptor activation and blockade on BLA pyramidal cells under normal conditions and in an arthritis pain model. AAV5.CamKII.GCaMP6f.WPRE.SV40 was injected stereotaxically into the rat BLA to express a calcium indicator (GCaMP6f) selectively in excitatory BLA neurons. Two-photon calcium imaging was conducted in brain slices from normal rats and from arthritic rats (5-6 h after intraarticular injections of kaolin and carrageenan into the left knee). Calcium responses were evoked by electrical synaptic stimulation of LA-BLA connections or of the external capsule (EC). Synaptic stimulation evoked calcium responses in subsets of BLA neurons. Application of a CB1 receptor agonist (ACEA) had mixed effects under normal conditions, increasing and decreasing calcium responses in different subsets of BLA neurons. In the arthritis pain model, the predominant effect of ACEA on calcium signals was facilitatory. A CB1 receptor antagonist (AM251) had no significant effect on calcium responses to baseline synaptic stimulation under normal conditions and in the arthritis model. The results suggest heterogeneity among BLA neurons with regard to their endocannabinoid modulation but there is evidence for facilitatory function in the arthritis pain model.

Disclosures: **T. Kiritoshi:** None. **V.A. Yakhnitsa:** None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Amygdala cannabinoid CB1 modulation of pain behaviors in a rodent model of arthritis pain

Authors: *M. HEIN[1], J. M. THOMPSON[1], V. NEUGEBAUER[1,2]
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Pain is an unpleasant sensory experience with significant emotional affective components. The amygdala is a limbic structure that is involved in emotional affective aspects of pain. Specifically, hyperactivity in the basolateral-central amygdala (BLA-CeA) network drives emotional responses and anxiety-like behavior in pain models. The cannabinoid receptor 1 (CB1), a $G_{i/o}$ protein-coupled receptor, is expressed on GABAergic interneurons in the basolateral amygdala (BLA). Preclinical studies have demonstrated antinociceptive effects of CB1 receptor activation in different areas of the nervous system, but the role of CB1 receptors in amygdala in pain behaviors remains to be determined. Here we test the hypothesis that CB1 receptor activation in the BLA increases pain behaviors and inhibition inhibits pain behaviors in a rodent model of acute arthritis pain. Audible (nocifensive response) and ultrasonic (affective response) vocalizations evoked by brief noxious stimulation of the left knee and mechanical sensitivity (hindlimb withdrawal reflex thresholds) were measured in adult rats before and 6 h after induction of a monoarthritis in the left knee by intra-articular injections of kaolin and carrageenan. Stereotaxic administration of a CB1 receptor agonist (ACEA) into the BLA by microdialysis had no effect under normal conditions but increased vocalizations in the arthritis model. Administration of a CB1 receptor antagonist (AM251) into the BLA had some facilitatory effects on vocalizations under normal conditions but decreased vocalizations in the arthritis model. Mechanical thresholds were unaffected by either agent under normal and arthritic conditions. The data suggest that CB1 receptors are endogenously activated under normal conditions and in a pain model, but they undergo a functional change by shifting from providing an inhibitory tone to facilitation in the pain state.

Disclosures: M. Hein: None. **J.M. Thompson:** None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Fear extinction learning ability predicts neuropathic pain behaviors and amygdala activity

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Abstract: Pain and fear may share neurobiological mechanisms such as plasticity in emotional networks. The amygdala plays a key role in fear conditioning and has emerged as an important node of emotional-affective aspects of pain and pain modulation. Pain is significantly associated with anxiety and depression and can impair prefrontal cortical function and control of amygdala output. Impaired fear extinction learning, which involves prefrontal cortical control of amygdala processing, has been linked to posttraumatic stress disorder (PTSD). Here we tested the hypothesis that fear extinction learning ability can predict the magnitude of neuropathic pain. We correlated fear extinction learning in adult male rats with behavioral outcome measures (sensory thresholds, vocalizations, anxiety- and depression-like behaviors) before and after induction of neuropathic pain (spinal nerve ligation model). Auditory fear conditioning, extinction and extinction retention tests were conducted using two chambers. On Day 1, rats were habituated to context A followed by fear conditioning (2 US-CS pairs). On Day 2, rats were habituated to context B followed by extinction training (30 CSs). On Day 3, rats were habituated to context B followed by extinction retention (5 CSs). The majority (80%) of rats showed a quick decline of freezing level during extinction training and retention (FE+) whereas 20% of the rats maintained a high freezing level (FE-). FE- rats showed decreased open-arm preference in the elevated plus maze (EPM), reflecting anxiety-like behavior, but there were no significant differences in sensory thresholds, vocalizations, or depression-like behavior (forced swim test, FST) between FE+ and FE- types. After induction of the neuropathic pain model, FE- rats developed a greater increase in vocalizations and anxiety- and depression-like behaviors than FE+ rats. Extracellular single unit recordings of CeA neurons in the same rats showed greater increases in background activity and in responses to innocuous and noxious mechanical stimuli (compression of the hindpaw with a calibrated forceps) in the FE- than FE+ type. The data may suggest a positive correlation between extinction learning ability and neuropathic pain control through a mechanism that involves the amygdala.

Disclosures: G. Ji: None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Group II mGluRs in amygdala contribute to the systemic effects of group II agonists on spinal nociceptive processing in an arthritis pain model

Authors: *V. NEUGEBAUER[1,2], M. MAZZITELLI[1]
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Pain is characterized by its negative affective component. The amygdala is an important contributor to pain-related emotional-affective disorders and pain modulation. G protein-coupled metabotropic glutamate receptors (mGluRs) participate in nociceptive processing and pain mechanisms at the peripheral, spinal and supraspinal levels. Group II mGluRs (mGluR2 and mGluR3) are highly expressed in limbic regions such as the amygdala. They are typically localized presynaptically and inhibit the release of neurotransmitters. Group II agonists have anxiolytic effects in the amygdala and also inhibit spinal nociceptive processing. Here we evaluated the contribution of group II mGluRs in the amygdala to the effect of systemic group II agonists on spinal cord activity in an arthritis pain model. Extracellular single unit recordings were made from spinal (L2-4) wide dynamic range (WDR) neurons, which respond to innocuous and noxious stimuli, in adult normal rats and arthritic rats (5-6 h postinduction of a kaolin/carrageenan-monoarthritis in the left knee). A group II mGluR agonist (LY379268 disodium salt) was applied systemically (intraperitoneally (i.p.) during the electrophysiological recording and the drug effect was evaluated for 90 min. To determine the contribution of the amygdala, a group II mGluR antagonist (LY341495 disodium salt) or a positive allosteric modulator (PAM) selective for mGluR2 (LY487379 hydrochloride) was administered stereotaxically into the right central nucleus of amygdala (CeA) by microdialysis. All spinal WDR neurons had receptive fields in the ipsilateral knee joint and responded more strongly to noxious than innocuous mechanical stimuli. Systemic application of a group II agonist (LY379268) decreased the responses of WDR neurons to mechanical stimuli in arthritic rats. This effect was reversed by the co-administration of a group II antagonist (LY341495) into the CeA. An mGluR2 PAM (LY487379) administered alone into the CeA also inhibited neuronal activity in the spinal cord in the arthritis pain model. These results suggest that group II mGluRs in the amygdala can modulate spinal nociceptive processing and contribute to the effects of systemically applied group II agonists.

Disclosures: V. Neugebauer: None. **M. Mazzitelli:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Overexpression of potassium (SK) channels in the amygdala in a rat model of neuropathic pain inhibits neuronal excitability and pain behaviors

Authors: *V. A. YAKHNITSA[1], J. M. THOMPSON[1], V. NEUGEBAUER[1,2]
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Treatment of chronic pain, including neuropathic pain, remains a clinical challenge. Therapeutic strategies are limited by severe side effects and by limited efficacy on emotional-affective aspects of chronic pain. The amygdala is a limbic brain region that plays a key role in mediating the emotional affective component of pain. Our previous work showed that increased activity in output neurons of the central nucleus of the amygdala (CeA) in pain models drives emotional-effective responses and anxiety-like behaviors. Increased activity of CeA neurons may be triggered by dysfunction of small-conductance calcium-activated potassium (SK2) channels. Here we tested the hypothesis that overexpression of SK2 channels in the CeA would inhibit pain-related changes in amygdala output neurons, resulting in the inhibition of pain behaviors in a rat model of neuropathic pain (L5 spinal nerve ligation, SNL). To rescue SK2 channel function, an AAV viral vector construct with synapsin promoter-driven expression of the tetracycline transactivator protein and tet-CMV promoter-driven expression of SK2 channels was injected into the CeA. Behavioral measurements and brain slice physiology were done in SNL rats and sham controls 4 weeks after surgery. Whole-cell voltage- and current-clamp recordings of regular firing CeA neurons in brain slices from SNL rats showed reduced mAHP and increased action potential frequency-current (F-I) relationships, which corresponded to increased vocalizations, mechanical sensitivity (von Frey test), and depression-like behaviors (sucrose preference) compared to control rats. Viral-vector mediated SK channel expression (3 weeks after AAV injection into the right CeA) restored the apamin-sensitive mAHP and inhibited excitability (F-I relationship) in CeA neurons, which corresponded to decreased vocalizations, mechanical sensitivity, anxiety-like (elevated plus maze) and depression-like (sucrose preference) behaviors compared to SNL rats without AAV vector treatment. The results provide evidence for the direct involvement of SK2 channels in the regulation of amygdala activity and neuropathic pain-related behaviors.

Disclosures: V.A. Yakhnitsa: None. **J.M. Thompson:** None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Optogenetic stimulation of amygdala CRF neurons modulates spinal nociceptive processing in an arthritis pain model

Authors: *M. MAZZITELLI[1], V. NEUGEBAUER[1,2]
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The central nucleus of amygdala (CeA) plays an important role in emotional-affective aspects of pain and modulation of pain sensitivity. The CeA receives pain-related information through projections from the basolateral amygdala (BLA) and the brainstem. A subset of CeA neurons are “projection neurons” that contain corticotropin releasing factor (CRF); one of their targets is the descending pain modulatory system that regulates spinal nociceptive processing, but the effect of amygdala output on the activity of spinal neurons remains to be shown. Here we focused on the effects of optogenetic activation or silencing of CRF-CeA neurons and BLA-CeA projections on spinal neurons. Extracellular single unit recordings were made from spinal (L2-4) wide dynamic range (WDR) neurons, which respond to innocuous and noxious stimuli, in adult normal rats and arthritic rats (5-6 h postinduction of a kaolin/carrageenan-monoarthritis in the left knee). For optogenetic activation or silencing of CRF neurons, a Cre-inducible viral vector (DIO-AAV) encoding channel rhodopsin 2 (ChR2) or enhanced Natronomonas pharaonis halorhodopsin (eNpHR3.0) was injected stereotaxically into the right CeA of transgenic Crh-Cre rats. For optogenetic activation or silencing of BLA axon terminals in the CeA, a viral vector (AAV) encoding ChR2 or eNpHR3.0 under the control of the CaMKII promoter was injected stereotaxically into the right BLA of Sprague-Dawley rats. For wireless optical stimulation of ChR2 or eNpHR3.0 expressing CRF-CeA neurons or BLA-CeA axon terminals, an LED optic fiber was inserted into the CeA on the day of the experiment. All spinal WDR neurons had receptive fields in the ipsilateral knee joint and responded more strongly to noxious than innocuous mechanical stimuli. Optical activation of CRF-CeA neurons or of BLA axon terminals in the CeA increased the responses of spinal WDR neurons under normal condition. Conversely, optical silencing of CRF-CeA neurons or of BLA axon terminals in the CeA decreased the responses of spinal WDR neurons in the arthritis pain model. These findings suggest that the amygdala can regulate the activity of spinal cord neurons under normal conditions and in a pain model, and that CeA output correlates positively with spinal nociceptive processing.

Disclosures: M. Mazzitelli: None. **V. Neugebauer:** None.

Poster

144. Descending Modulation of Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 144.09/DD32

Topic: D.03. Somatosensation: Pain

Title: Analysis of the role of Glutamatergic and GABAergic periaqueductal gray (PAG) neuronal subpopulations in a mouse model of persistent inflammatory pain

Authors: *J. G. GRAJALES-REYES[1], V. K. SAMINENI[2], B. A. COPITS[2], D. E. O'BRIEN[3], S. SUNDARAM[2], A. M. GOMEZ[2], M. R. BRUCHAS[2], R. W. GEREAU, IV[2]
[2]Anesthesiol., [1]Washington Univ. Sch. of Med., Saint Louis, MO; [3]Anesthesiol., Washington Univ. Sch. of Med., St Louis, MO

Abstract: It has been estimated that 100 million adults suffer from chronic pain in the United States, with an annual societal cost of approximately 600 billion dollars. Endogenous analgesic pathways represent an alternative route for the development of new therapies. Pharmacological and electrical stimulation studies of the ventrolateral periaqueductal gray (vlPAG) have implicated its role in descending pain modulation. The GABA disinhibition hypothesis put forward by Basbaum and Fields proposes that tonic GABAergic neurotransmission at the level of the vlPAG serves to inhibit output excitatory projections that mediate descending analgesia, and disinhibition of vlPAG excitatory neurons that project to the rostral ventromedial medulla (RVM) is thought to allow subsequent activation of RVM cells that project to the dorsal horn of the spinal cord and inhibit nociceptive transmission. Numerous lines of evidence are consistent with this hypothesis, but experimental manipulations used in prior studies lack cell-type specificity, preventing unambiguous determination of the role of specific subsets of vlPAG neurons in analgesia. Techniques such as chemo- and opto-genetics now afford us the opportunity to selectively manipulate identified subclasses of vlPAG neurons. With the GABA disinhibition hypothesis as our model, we hypothesized that stimulation of excitatory vlPAG neurons or a reduction of in vlPAG GABAergic tone would result in analgesia. We find chemogenetic stimulation of glutamatergic neurons or inhibition of GABAergic vlPAG neurons results in an elevation of withdrawal thresholds to noxious stimuli in naïve animals. In the context of persistent inflammatory pain, we find that optogenetic stimulation of Vglut2 or chemogenetic inhibition of Vgat vlPAG neurons results in attenuation of inflammation-induced hyperalgesia. Using an intersectional genetic approach, we provide direct experimental evidence for the proposed analgesic role for glutamatergic projections from the PAG to the RVM. In brief, our findings support the GABA disinhibition hypothesis, highlighting the role of local tonic GABAergic neurotransmission as an analgesic gatekeeper at the level of the vlPAG.

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Poster

144. Descending Modulation of Pain

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NIH R01NS048602

Title: Central amygdala neurons modulate pruritic processing

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Abstract: Itch is defined as an unpleasant sensation that evokes a desire to scratch. Recently, a surprising diversity of the sensory and spinal cord dorsal horn neurons that specifically process pruritic stimuli has been discovered. Despite this knowledge, our understandings of supraspinal mechanisms that are engaged in the itch processing are largely unknown. Here we took an unbiased approach using immediate early gene (cFos) mapping for precise dissection of brain circuits that mediate itch processing. These studies identified the central nucleus of the amygdala (CeA) as a region robustly engaged during itch/scratching. We manipulated the activity of these itch responsive neurons in the CeA using optogenetics or chemogenetics to study the role of these neurons in pruritus. Engineered excitatory (Gq) or inhibitory (Gi) GPCRs (DREADDs) or ChR2 were expressed in functionally-defined itch-responsive CeA neurons via adeno-associated viral vectors. We found that activation of itch responsive neurons in the CeA enhanced itch-like behaviors, while inhibiting these neurons reduced itch-like behaviors. Furthermore, we find that chloroquine-induced itch leads to robust aversion in a place preference assay, and suppressing the activity of the itch-activated CeA neurons eliminates this aversion. Taken together, these data suggest that CeA neurons are part of a brain circuit involved in the modulation of pruritic processing, and reveal clear roles for these neurons in both sensory and affective aspects of itch.

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Poster

144. Descending Modulation of Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 144.11/DD34

Topic: D.03. Somatosensation: Pain

Support: NSERC

Title: Continuous modulation of spinal cord function in relation to the affective component of pain assessed with fMRI

Authors: *P. W. STROMAN, J. M. POWERS, G. IOACHIM
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Abstract: Pain elicited by a noxious sensation depends on the intensity of the sensation, and emotional and cognitive factors, via descending signaling from the brainstem to regulate spinal cord responses. Inputs to the spinal cord are both pro- and anti-nociceptive and the net balance alters pain in relation to factors such as salience, anticipation, placebo, etc. It is expected that many chronic pain conditions involve an imbalance of this regulation.
We have previously investigated descending pain regulation using functional magnetic resonance imaging (fMRI) in the brainstem (BS) and spinal cord (SC) and have identified both reactive, and continuous, responses when human research participants were prompted to anticipate a stimulus. The continuous component corresponds with cognitive/affective influences on pain sensitivity and occurs both before and after stimulation. In order to further investigate this continuous component of descending regulation we hypothesized that it contributed to blood oxygenation-level dependent (BOLD) signal variations in prior fMRI studies involving heat pain, and that it gives rise to coordinated signal variations between BS/SC regions.
Data from 56 healthy participants were taken from prior studies which used similar pain stimulation conditions. The data were pre-processed to correct for motion, remove physiological noise, and were spatially normalized. The BOLD responses that are synchronous with noxious heat stimulation were modelled and subtracted from the data. This is to remove the sensory/discriminative component of the pain response, leaving the continuous component (i.e. cognitive/affective).
Data were analyzed using dynamic structural equation modeling (SEM) based on an established anatomical model of BS/SC regions involved with pain responses. SEM was applied to the data for each participant, and connectivity strengths between regions at different times during the stimulation paradigm (before, during, after stimulation) were analyzed in relation to individual pain ratings.
The results demonstrate significant connectivity across BS/SC regions, and connectivity strengths between a number of regions were correlated with pain ratings. These connections were

predominantly inputs to the periaqueductal gray matter (PAG) and rostral ventromedial medulla (RVM), which are known to be involved with descending pain regulation. These findings suggest that this contribution is a common occurrence in pain fMRI studies. Moreover, they demonstrate a method of characterizing descending regulation involved with the cognitive/affective component of pain, and may provide insight into chronic pain conditions.

Disclosures: P.W. Stroman: None. **J.M. Powers:** None. **G. Ioachim:** None.

Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR057194

Title: Opposing effects of cervical spinal cold block on spinal itch and pain transmission

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Abstract: Inactivation of descending pathways largely enhanced responses of spinal dorsal horn neurons to noxious stimuli, but little is known regarding tonic descending modulation of spinal itch transmission. We investigated effects of cervical spinal cold block on responses of dorsal horn neurons to itch- and pain-evoking stimuli. In pentobarbital-anesthetized mice, single-unit recordings were made from superficial dorsal horn neurons (depth: 153+/-10 μm). Responses were recorded to noxious heat, brush, touch, histamine (50 μg/μL id), chloroquine (100 μg/μL id), and allyl isothiocyanate (AITC, 70% topical). 64 units were tested (46% wide dynamic range-type, 54% nociceptive-specific). Cold block had no effect on mechanically-evoked responses. Ten units' responses to noxious heat were significantly enhanced (151% of control) during cold block, while 6 units' responses were reduced (62.2% of control) and the remainder (n=18) unaffected. 26 units responded to AITC, with a further significant increase in firing during the 1-min period of cold block beginning 1 min after AITC application. Activity during cold block was significantly greater compared to the same time period of control responses to AITC in the absence of cold block (n=39). Id histamine excited 17 units. Cold block starting 1 min after id injection of histamine caused a marked decrease in firing. The histamine-evoked response during and following cold block was significantly lower compared to control histamine-evoked responses in the absence of cold block (n=57). A similar but weaker depressant effect of

cold block was observed for dorsal horn unit responses to chloroquine (n=26), for which chloroquine-evoked activity during cold block was lower compared to that seen for control responses in the absence of cold block (n=25). These results indicate that spinal chemonociceptive transmission is under tonic descending inhibitory modulation, while spinal pruriceptive transmission is under an opposing, tonic descending facilitatory modulation.

Disclosures: E.E. Carstens: None. **M. Iodi Carstens:** None. **A. Davoodi:** None. **M. Nagamine:** None. **T. Akiyama:** None.

Poster

144. Descending Modulation of Pain

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Program#/Poster#: 144.13/DD36

Topic: D.03. Somatosensation: Pain

Title: Vagal afferent regulation of the descending analgesia system: A novel mechanism regulating vagal and nociceptive reflexes

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Abstract: The submedius nucleus of the thalamus (SubM), ventrolateral orbital cortex (VLO) and periaqueductal grey (PAG) constitute a well-described pain modulatory pathway. Activation of this pathway leads to depression of nociceptive inputs in the spinal cord dorsal horn via the rostromedial medulla and the brainstem descending inhibitory system. Using transynaptic anterograde viral tracing in Sprague Dawley rats, we noted a neural circuit derived from jugular ganglia vagal afferents innervating the respiratory tree projecting to neurons in the SubM, suggestive that vagal afferent pathways may be similarly regulated by the SubM-VLO-PAG descending modulatory system. As expected, anterograde neuronal tracing with biotinylated dextran amine (n=4) revealed strong projections from the SubM to the VLO. In functional studies using urethane anesthetized rats, electrical stimulation of the larynx to activate vagal afferent fibres evoked respiratory slowing in a stimulus frequency dependent manner. Concomitant activation of the SubM via bilateral microinjections of 5ug serotonin significantly inhibited reflex reductions in respiration when compared to vehicle controls (e.g., from a baseline respiratory rate of 117±4.7 breaths per minute (bpm), to 12±2.2 bpm and 69±5.9bpm in vehicle and serotonin treated animals, respectively and; p=0.0001, n=9/ group). The inhibitory effect induced by SubM activation was absent in animals receiving prior electrolytic lesion of the VLO. Moreover, lesion of the VLO facilitated the respiratory slowing caused by laryngeal stimulation, consistent with a tonic descending inhibitory influence over respiratory vagal afferent processing. None of the interventions altered baseline breathing, indicative of a selective

influence over vagal afferent processing and not bulbar respiratory motor pattern generation. Taken together, these data support the notion that the SubM-VLO-PAG descending modulatory system plays an import role in the regulation of bulbar visceral afferent processing. Furthermore, the data may provide a circuit framework that explains the well described suppression of spinal nociceptive processing induced by vagus nerve stimulation.

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Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant AR057194

Title: Effects of pruritogens and algogens on rostral ventromedial medullary (RVM) ON and OFF cells

Authors: ***M. IODI CARSTENS**[1], E. E. CARSTENS[2], T. AKIYAMA[4], T. FOLLANSBEE[5], M. FUJII[3], A. DAVOODI[5], M. NAGAMINE[5]
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Abstract: RVM ON- and OFF cells are thought to facilitate and inhibit spinal nociceptive transmission, respectively. However, it is unknown how ON and OFF cells respond to pruritic stimuli or how they contribute to descending modulation of spinal itch signaling. In pentobarbital-anesthetized mice we thus recorded responses of RVM ON and OFF cells to pruritic, algesic and scratch stimuli. Single-unit recordings were made in RVM from ON and OFF cells identified by their respective increase or decrease in firing that occurred just prior to nocifensive hindlimb withdrawal elicited by paw pinch. Of RVM ON cells, 86% (24/28) were excited by intradermal (id) histamine (50 μg/μL), 50% by id chloroquine (100 μg/μL), and 76% by id capsaicin. All units also responded to a scratch stimulus applied adjacent to the hindpaw injection site. Most units were unresponsive to id injection of vehicle, but still responded to scratching. More variable effects were observed with OFF cells. Id histamine and scratching excited 50% while inhibiting or having no effect in the remainder. Id chloroquine was ineffective in 62% while exciting 15% and inhibiting 23%. Id capsaicin and scratching inhibited 64% while exciting 14% and having no effect in the remainder. These results indicate that ascending

pruriceptive signals may activate RVM ON cells to initiate descending facilitation of spinal itch and pain transmission. The mainly inhibitory effect of capsaicin on OFF cells is consistent with decreased descending inhibition to facilitate spinal nociceptive transmission. The mixed effects of pruritogens on OFF cells suggests a more complex descending modulatory effect on spinal pruriceptive transmission that may include descending inhibition (by excitation of some OFF cells) that counteracts descending facilitation (by inhibition of OFF cells and excitation of ON cells).

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Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: VA M.R. award 1I01RX001776

DoD award MR130295

Title: The role of descending serotonin signaling on nociceptive sensitization after mild traumatic brain injury

Authors: *P. SAHBAIE[1,2], M. TAJERIAN[1,2], D.-Y. LIANG[1,2], K. A. IRVINE[1,2], J. D. CLARK[1,2]
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Abstract: Mild traumatic brain injury (mTBI) consequent to war related injuries, falls or motor vehicle accidents accounts for about 80% of all TBIs. mTBI which is commonly due to closed head concussive impact injuries leads to chronic disability and is often accompanied by chronic pain. Chronic pain associated with mTBI is challenging to manage and hinders rehabilitation efforts. Specific treatments for TBI-related pain is lacking partly due to gaps in understanding underlying mechanisms of mTBI related chronic pain development. Many mTBI or chronic pain patients suffer long-lasting neurobehavioral impairments. In addition, many polytrauma patients (injury to at least two body regions) suffer from chronic pain. Previously we had shown that concussive mTBI resulted in nociceptive and working memory alterations, a useful preclinical model for studying TBI and chronic pain. Here we went on to characterize the nature of nociceptive alterations in mild TBI by pharmacological means. Nociceptive sensitization to mechanical stimuli was measured and Diffuse Noxious Inhibitory Controls (DNIC) was assessed immediately after forepaw capsaicin application. Lateral closed cortical impact mTBI resulted in

hindlimb mechanical allodynia lasting 14 days. mTBI resulted impaired DNIC after local PGE2 application. Further investigation revealed that interference with systemic and spinal serotonin signaling ameliorated nociceptive sensitization observed after TBI. Systemic depletion using p-Chlorophenylalanine or spinal application of 5,7-Dihydroxytryptamine resulted in decreased mechanical hypersensitivity after TBI. Additionally, spinal application of ondansetron 72 hours after TBI resulted in decreased hypersensitivity also. Findings presented in our study provide evidence for a central role of descending modulatory signaling in pain sensitization after closed head TBI.

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Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant (1R01DE022129)

Title: Analgesic effect of electrical stimulation of the lateral habenula (LHb)

Authors: *A. S. PARCHURE[1], H. N. HARRIS[1], Y. B. PENG[2]
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Abstract: Local field potential (LFP) is a collective neural signal of all the synaptic activity occurring at a specific area of the brain, thereby offering a unique insight into how the brain functions. The habenula is involved in the pain pathway and decision-making. Located above the thalamus, it has been proposed to function with nucleus accumbens and periacqueductal gray (PAG) along with other regions in a descending pain modulation pathway. The main purpose of the present study was to determine the contribution of LHb to the nociceptive input and the effect of activation on antinociception. One week after implantation of electrode in the LHb in adult Sprague Dawley male rats (n=16), formalin was injected in the right hind paw, LFP recordings were recorded at baseline and post-formalin. Electrical stimulation was delivered to the LHb, and LFP were recorded in these freely moving animals. Animals were also subjected to mechanical and thermal paw withdrawal tests to assess the change of nociception and LFP responses. LFP were analyzed by power spectrum analysis. The results showed that: (1) Behaviorally, significant decrease in paw withdrawal threshold and latency were observed after formalin injections ($p < .05$), indicating increase in nociception. Interestingly, electrical stimulation of LHb has significantly reversed the phenomena, suggesting an antinociceptive role by LHb. (2)

Simultaneously, we observed significant increase for the LFP powers during formalin period ($p < .05$) in response to mechanical and thermal stimuli, which were reduced by electrical stimulation of LHb ($p < .05$). (3) There was a trend of significant increase for all the frequency bands following formalin injection ($p < .05$) comparing to the baseline. The possible explanation is that the increased activity in habenula is due to increased inputs from the lateral hypothalamus and the spinal cord, which are part of the neural circuitry involved in pain transmission. (4) Following LHb electrical stimulation, significant decreases of the LFP power in different frequency bands were also observed ($p < .05$). Since LHb projects further into ventral tegmental area (VTA, the substantia nigra (SNc), dorsal raphe, and PAG, which are important structures in descending modulation of pain, electrical stimulation of habenula may activate the descending inhibitory system to achieve the analgesic effect. In conclusion, formalin-induced inflammatory nociception increases the LFP recordings in the habenula while electrically stimulating this region induce an antinociceptive effect which was also observed via both behavioral and electrophysiological tests.

Disclosures: **A.S. Parchure:** None. **H.N. Harris:** None. **Y.B. Peng:** None.

Poster

144. Descending Modulation of Pain

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Title: The parabrachial complex directly link pain transmission to pain modulation via a direct connection to the rostral ventromedial medulla

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Abstract: An important factor in both normal and clinically significant pain is the intrinsic pain-modulating system, which regulates nociceptive processing via projections from the brainstem to the dorsal horn. The output of this modulating system, the rostral ventromedial medulla (RVM), can facilitate or suppress nociceptive transmission at the dorsal horn by the respective action of two distinct classes of neurons, “ON-cells” and “OFF-cells.” Both classes respond to noxious inputs: ON-cells are activated, leading to a “burst” of activity associated with behavioral responses to noxious stimulation, whilst OFF-cell firing is suppressed, producing a “pause” in

any ongoing activity. However, the pathway through which noxious inputs drive changes in RVM activity is only now being defined. Anatomically, the RVM receives direct spinoreticular and trigeminal reticular inputs, as well as afferents from the parabrachial complex (PB), which is the major target of supraspinal projections from the superficial dorsal horn. A direct projection from PB to RVM has been identified, but its functional roles have not studied. Optogenetic activation of PB terminals expressing channelrhodopsin (ChR2) in whole-cell patch-clamp experiments in an RVM slice revealed both glutamatergic and GABAergic inputs to RVM neurons from PB. *In vivo* studies confirmed that both ON- and OFF-cells can be excited or inhibited by global activation of PB terminals in the RVM. Cell response latency to light stimulation of PB terminals suggests direct synapses to ON and OFF cells. Furthermore, archaerhodopsin (ArchT)-induced inhibition of PB terminals significantly attenuated the reflex-related activity of ON- and OFF-cells, and produced behavioral antinociception. These data show that a substantial component of the relevant nociceptive drive to RVM pain-modulating neurons is relayed through PB via a direction projection. Reflex-related changes in firing of these neurons thus depend on a short intrabrainstem loop conveying information related to noxious stimuli. Furthermore, the dual nature of PB inputs to RVM has the potential to support plasticity in acute and chronic pain. While the PB is well known as an important relay for ascending nociceptive information, the direct connection with the RVM allows the spinoparabrachial pathway to access descending control systems as part of a positive or negative feedback circuit.

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Poster

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DE025137

Title: Optogenetic Dissection of descending 5HT-containing neuron function in normal and persistent pain conditions

Authors: *J. YANG, J. LEE, J. WANG, J. ASGAR, W. GUO, C. BIAN, S. ZOU, R. DUBNER, K. REN, F. WEI

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Abstract: The rostral ventromedial medulla (RVM) provides major descending projections to modulate nociceptive input and transmission in spinal and trigeminal dorsal horn. Although functional subpopulations of RVM neurons in descending pain modulation have been characterized, 5-HT-containing neurons are best known as being descending neurochemical projections. Accumulating data indicate that active 5-HT-dependent descending facilitation is implicated in the maintenance of persistent pain. However, it is less known whether activation of 5-HT-containing neurons alone in the RVM sufficiently produces behavioral pain responses or active 5-HT-containing RVM neurons are required for persistent pain after nerve injury. By SERT cre mouse line with optogenetics, we specifically manipulated endogenous serotonergic activity in the RVM to dissect its role in descending pain modulation. First, we observed opsin expression in the RVM of SERTcre mouse after microinjection of Cre-dependent AAV9-ChR2-mCharry. Immunostaining showed that most of ChR2-mCharry-expressing cells are serotoninergic and the infected soma are selectively distributed in the RVM. About 80% of 5-HT-immunoreactive neurons per section of the RVM expressed ChR2. After implanting an optical fiber precisely targeting the RVM, we examined the effects of blue light stimulation to ChR2-expressing 5-HT neurons on normal nociception in freely moving animals. Single optical stimulation produced significant mechanical allodynia and thermal hyperalgesia in hindpaw or orofacial skin over 24 hr and conditioned place avoidance on the next day. Robust expression of c-Fos in RVM neurons including 5-HT-containing neurons after light stimulation indicates effective excitation of the RVM 5-HT system. Surprisingly, only a few c-Fos-labelled neurons were observed in the superficial layers of the dorsal horn. Molecular depletion of 5-HT from the RVM with local Tph-2 shRNA prevented light-induced behavioral hypersensitivity. These results confirm previous finding that selectively transient activation of 5-HT-containing RVM neurons in normal animals produces prolonged pain behavior. Next, we investigated the effects of inhibition of 5-HT-containing neurons in the RVM on trigeminal neuropathic pain induced by chronic constriction injury of the infraorbital nerve (CCI-ION). Optogenetic inhibition of RVM 5-HT-containing neurons with intra-RVM injection of AAV9-eNpHR3.0-eYFP attenuated behavioral hypersensitivity strongly at 14 d but less at 5d after CCI-ION, further supporting that active 5-HT-dependent descending facilitation is responsible for the transition of acute pain to chronicity.

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Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NIH NCCIH Intramural

Title: Novel sensory measurement of placebo analgesia

Authors: L. K. CASE[1], C. M. LAUBACHER[1], E. A. RICHARDS[1], M. GROSSMAN[1], L. Y. ATLAS[1], S. PARKER[2], *M. C. BUSHNELL[1]
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Abstract: There is ongoing debate about whether placebo analgesia alters sensory nociception or whether it merely alters cognitive processing. Because pain is a subjective experience, placebo analgesia effects are almost always quantified using verbal or written perceptual reports. As such, they are susceptible to conscious and unconscious response bias related to demand characteristics of the experiment (Zellner et al. 2004). In other words, subjects may report reduced pain because they believe they should be experiencing reduced pain, not because their sensory pain experience has changed. Past research suggests that both sensory effects and response bias may contribute to the placebo effect. However, a behavioral measure of the sensory component of the placebo effect, devoid of cognitive bias, has not previously been available. We devised a novel behavioral test of the sensory component of the placebo effect. Our task relies on the premise that discriminating between two temperatures should be more difficult if the hotter temperature is applied to the placebo arm (where the placebo effect should effectively reduce the perceived temperature and hence the perceived difference) and easier if the hotter stimulus is applied to the control arm (where the placebo effect on the other arm effectively further reduces the lower temperature, increasing the perceived difference). Our placebo testing procedure was designed to minimize the influence of response bias, as accurate sensory discrimination depends on unbiased sensory perception. Perhaps owing to this minimization of experimental demand, we observed a low rate of placebo response. However, our analyses were powered to measure placebo effects within single subjects. Of the two participants who showed a placebo response in ratings, one showed a clear sensory discrimination placebo effect and the other showed a weak effect. Of the six who did not show a placebo response in ratings, only one subject showed a weak sensory discrimination placebo effect. Our results support the hypothesis that placebo analgesia can alter sensory perception, but suggest that it does not always do so. Further, we report dissociations between subjective ratings of placebo effect and our novel sensory discrimination measure of placebo response.

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Poster

144. Descending Modulation of Pain

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Topic: D.03. Somatosensation: Pain

Support: NSERC

Title: The modulatory effect of emotion on brainstem pain signaling pathways

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Abstract: Pain is a subjective unpleasant experience that is comprised of both sensory and affective components. Emotion is thought to modulate pain perception through descending inhibition mediated by specific brainstem structures. The neural mechanism has not been observed in live, conscious humans, as most studies have been conducted in animals and tissue preparations. Human pain research is necessary to account for cognitive and emotional factors that may modulate pain perception. Functional magnetic resonance imaging (fMRI) is a powerful neuroimaging tool that allows for analysis of dynamic changes in metabolic activity as a response to pain stimulation.
The purpose of this study was to determine the modulatory effect of emotion on brainstem pain signaling pathways. We hypothesize that as part of the limbic system, hypothalamic input will decrease pain perception when a person is in a positive emotional state. This was tested using fMRI data from three previous pain studies, and structural equation modeling (SEM). The model uses a multi-linear regression to approximate the covariance between blood-oxygen-level-dependent (BOLD) signal changes between two or more brainstem areas. A control study without emotional modulation was compared against two studies with emotional modulation of evoked heat pain. SEM was used to model significant networks of connections between the hypothalamus (Hyp), periaqueductal gray (PAG), nucleus raphe magnus (NRM) and nucleus tractus solitarius (NTS), areas directly connected and involved in emotional processing. Results of the analysis indicate that emotion may modulate pain perception through a Hyp□PAG connection present only in studies involving emotional modulation. Connectivity between areas in the chosen network was dynamic and varied across periods before, during and after pain stimulation, indicating more complex, coordinated activity than previously understood. In conclusion, these results provide a physiological basis for emotional modulation of pain, and suggest that the experience of pain is a continuum spanning the build-up to pain, the synchronous response to pain stimulation, and the alleviation from pain.

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Poster

144. Descending Modulation of Pain

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Title: Tropomyosin receptor kinase b receptor agonism reverses impairment of noradrenergic endogenous analgesia and enhances resolution from incisional pain in a rat model

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Abstract: Background: Impairment of endogenous analgesia plays important roles in acute and chronic pain. Recently, we have reported impairment of noradrenergic endogenous analgesia at a late stage following peripheral nerve injury, and treatment with amitriptyline reversed it. We hypothesized that this effect is partially mediated by brain derived neurotrophic factor (BDNF) signaling. The aims of this study are to examine the roles of endogenous analgesia in resolution from incisional pain in animals with long lasting neuropathic pain, and to examine the effect of TrkB receptor agonist, 7,8-dihydroxyflavone (DHF), on incisional pain.
Methods: Sprague-Dawley rats were received right L5/L6 spinal nerve ligation (SNL). From the 6th week following SNL, rats were administered DHF (5mg/kg/mL) or vehicle subcutaneously for 5 consecutive days. After the treatment, an incision was made on the skin and plantar muscle of the left hind paw. Mechanical hypersensitivity around the wound was assessed with von Frey filaments at the predetermined time points (before-SNL, 6^{th} week after SNL, post treatment, post incision day1 to 35). To examine the effect of DHF on noradrenergic descending inhibition, concentration of noradrenaline (NA) in the spinal dorsal horn was measured by microdialysis under anesthesia. Change in density of Dopamine beta hydroxylase (DβH) and alpha-2 adrenaline receptor (α2-AR) in the spinal dorsal horn was assessed by immunohistochemistry. Effect of DHF on morphine analgesia (10mg/kg intraperitoneally) for acute pain was examined at day1 after paw incision in different animals.
Results: SNL rats showed delayed recovery from incisional pain than the naïve rats, and DHF treatment in SNL rats restored the recovery. Microdialysis study revealed increase of NA after SNL compared with naïve animals, and DHF treatment in SNL rats decreased NA concentration to the level of naïve animals. DHF treatment did not affect the density of DβH and α2-AR either. SNL rats showed weaker analgesic effect of morphine on incisional pain than naïve animals, and

DHF treatment restored the attenuation of analgesic effect.
Conclusions: Animals at late stage following SNL showed slower recovery from incisional pain and less efficacy of morphine analgesia for acute incisional pain than naïve animals. DHF treatment provided beneficial effect on both changes. Based on our microdialysis study, chronic elevation of NA in spinal cord may reduce additional release of noradrenaline evoked by additional pain. DHF treatment may attenuate excessive activation of LC, and may restore margin for additional excitation.

Disclosures: T. Suto: None. **D. Kato:** None. **S. Saito:** None. **H. Obata:** None.

Poster

144. Descending Modulation of Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 144.22/EE9

Topic: D.03. Somatosensation: Pain

Support: NIH Grant NS065926

NIH grant NS098826

Title: Spinal D5 receptor drive the transition from acute to chronic pain

Authors: *S. MEGAT, P. BARRAGAN IGLESIAS, J. MOY, T. PRICE
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Abstract: Our previous work showed that descending dopaminergic projections, likely originating in the hypothalamic A11 nucleus, play a critical role in maintaining plasticity in hyperalgesic priming. Our findings suggested that spinal D1/D5 receptors were the key targets for these descending dopaminergic pathways and that these receptors play a prominent role in maintenance of plasticity after a transition to a chronic pain state. First, we find that a specific lesion of the dopaminergic neurons arising from the hypothalamic A11 nucleus prevents maintenance of hyperalgesic priming induced by an intrathecal injection of brain derived neurotrophic factor (BDNF). Moreover, intrathecal injection of a D1/D5 agonist, SKF-82958 precipitates priming in mice previously exposed to BDNF recapitulating our previous findings with interleukin 6 and carrageenan injection into the hindpaw. Then, using D5 receptor deficient mice, we show that carrageenan as well as IL-6-induced hyperalgesia is reduced in a sex-dependent manner. These data suggest that in primed mice, dopamine release from A11 neurons would potentially activate post-synaptic D5 receptors to maintain a primed state. Next, we sought to characterize neuronal activation in the spinal dorsal horn of primed and non-primed mice using an indirect marker of neuronal activity, c-fos. Our data show that intrathecal injection

of the D1/D5 agonist in primed mice activates a specific subset of neurons in the lamina III-IV of the spinal dorsal horn. These c-fos positive neurons co-express PAX2, a transcription factor known to be expressed in dorsal horn inhibitory interneurons. Consistent with a role for these neurons in pain promotion, we find that while GABA-A receptor agonists cause antiallodynia in naïve mice they are ineffective in primed mice. Moreover, GABA-A antagonists cause hyperalgesia in naïve mice but are antihyperalgesic in mice that have been primed and exposed to either peripheral prostaglandin E_2 (PGE_2) injection or spinal administration of a D1/D5 agonist. Our results support the hypothesis that D5 receptors exert a powerful influence over spinal cord circuitry involved in pathological pain via a GABAergic mechanism.

Disclosures: S. Megat: None. **P. Barragan Iglesias:** None. **J. Moy:** None. **T. Price:** None.

Poster

144. Descending Modulation of Pain

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Support: NIH/NIDA grant DA031777

Rita Allen Foundation

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Stanford Dean's fellowship

HHMI medical research fellowship

NDSEG fellowship

HHMI

Title: RVM GABAergic neurons command enkephalinergic spinal neurons to control mechanical pain

Authors: *A. FRANCOIS[1], S. LOW[4], E. SYPEK[5], A. J. CHRISTENSEN[6], C. SOTOUDEH[4], K. BEIER[2], C. RAMAKRISHNAN[4], K. RITOLA[7], R. SHARIF NAEINI[8], K. DEISSEROTH[9], S. L. DELP[3], R. C. MALENKA[10], L. LUO[11], A. HANTMAN[7], G. SCHERRER[1]
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Stanford Univ. Sch. of Med., Palo Alto, CA; [11]Howard Hughes Med. Inst. - Stanford Univ., Stanford, CA

Abstract: The spinal cord dorsal horn integrates information both from sensory neurons and the brain to shape pain experience. Specifically, populations of brainstem neurons in the rostral ventromedial medulla (RVM) project directly to the dorsal horn to facilitate or inhibit nociception as a function of emotional and internal states. This process is known as the descending control of pain. However, the stimuli and tasks that recruit RVM neurons to alter nociception in the dorsal horn, and the circuits involved, are largely unknown. Using viral tracing and electrophysiology, we identified a disynaptic brainstem-spinal cord circuit in which RVM neurons modulate enkephalin release in the dorsal horn to control pain. We found that a population of GABAergic neurons in the RVM inhibits spinal enkephalinergic interneurons in laminae I-III. We further demonstrate that these enkephalinergic neurons gate primary afferent inputs through temporally-coordinated presynaptic inhibition by enkephalins and GABA. Interestingly, despite their inhibitory nature, inhibition of these GABAergic RVM neurons facilitates pain, suggesting that they functionally correspond to a population of classical “ON cells”. To test this hypothesis, we use fiber photometry to record calcium activity in genetically defined population of RVM neurons in behaving mice submitted to a panel of sensory stimuli in different emotional and physiological states. These studies will identify the conditions in which these RVM neuron population are active and may modulate spinal enkephalin release to adjust pain thresholds. Our results identify the key components of a circuit and the molecular steps by which activity in the brain can cause pain facilitation at the level of the spinal cord by controlling spinal endogenous opioid levels.

Disclosures: A. Francois: None. **S. Low:** None. **E. Sypek:** None. **A.J. Christensen:** None. **C. Sotoudeh:** None. **K. Beier:** None. **C. Ramakrishnan:** None. **K. Ritola:** None. **R. Sharif Naeini:** None. **K. Deisseroth:** None. **S.L. Delp:** None. **R.C. Malenka:** None. **L. Luo:** None. **A. Hantman:** None. **G. Scherrer:** None.

Poster

144. Descending Modulation of Pain

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 144.24/EE11

Topic: D.03. Somatosensation: Pain

Support: NIH Grant (1R01DE022129)

Title: Local field potential of the periaqueductal gray during acute inflammatory pain

Authors: *H. N. HARRIS, A. S. PARCHURE, Y. B. PENG
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Abstract: Current methods of assessing pain are highly subjective. In searching for quantifiable indicators of pain, researchers have begun targeting neurosignatures from neuronal activity in the nociceptive pathway. A minimally invasive method is local field potential (LFP), which involves recording electrophysiological data from a representative collection of neurons within targeted brain regions (Buzsáki, 2004). Previous literature on this topic highlights top-down modulation of pain in decreases in oscillatory power (Hauck, 2015) In analyzing neuronal pain signaling, a likely source is the midbrain periaqueductal gray (PAG), for its known function of ascending and descending pain modulation between the spinal cord and the thalamus (Bushnell et al., 2013). The purpose of this study is to examine local field potential of the periaqueductal gray during acute inflammatory pain. The hypothesis of the current study is that the LFP will change in response to formalin injection. To test this hypothesis, electrodes were implanted into the left PAG of anesthetized male Sprague-Dawley rats. Ground and reference wires were attached to the skull, and a wireless recording module was attached to the implanted electrode in the PAG (5.3mm posterior to Bregma, .05 mm lateral to midline, and 5.3 mm depth; Paxinos & Watson, 1998). Local field potential was recorded for three minutes prior to pain induction to establish baseline synaptic activity. Rats were then given subcutaneous injections of .05mL of 3% formalin in the right hindpaw, and LFP was recorded for a time period of 60 minutes after injection. Spike 2 software was used to analyze artifact-free 60 s time bins taken at baseline, injection, and every 10 m after, with power spectrum analyses created from raw waveforms. Power spectrum data for each frequency band were normalized and then analyzed in SPSS with one-way repeated measures ANOVAs followed by Bonferonni post-hoc tests. Results show significantly different LFP activity from baseline after pain induction. There are increases in theta oscillations (at 50 and 60 minutes post-injection, $p < .05$), and decreases in delta (at 20, 30, 40, 50, and 60 minute post-injection, $p < .05$), alpha (at 10 minute post-injection, $p = .02$), gamma (at 60 minute post-injection, $p = .04$), and high gamma (at the injection time, 10, 30, 50, and 60 minute post- injection, $p < .05$). These findings are consistent with previous research indicating overall decreases in power during pain (Chen et al., 1983; Wang et al., 2015), suggesting top-down pain modulation in the region. In conclusion, local field potential in the periaqueductal gray can be integrated as part of neurosignature in pain activation.

Disclosures: H.N. Harris: None. **A.S. Parchure:** None. **Y.B. Peng:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: NIH AR068989

NIH NS055860

Title: *In vitro* glucocorticoid agonist fluticasone suppresses excitability of medium- to large-sized neurons in inflamed rat dorsal root ganglia

Authors: X. GONG, Z. SONG, J. STRONG, *J.-M. ZHANG
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Abstract: Epidural steroids are widely used for the treatment of various low back pain conditions. Their effects are attributed to activation of glucocorticoid receptors. However, clinically used steroids are non-selective and also activate mineralocorticoid receptors, which are expected to decrease the steroids' anti-inflammatory effect and may be responsible for clinical ineffectiveness in some patients. Fluticasone is a highly selective glucocorticoid receptor activator. Whether it affects neuronal excitability is unknown. We explored the effect of the fluticasone on whole dorsal root ganglion (DRG) neurons in which local inflammation had been induced by in vivo application of the immune stimulator zymosan to the L4/5 DRG (a model of chemogenic low back pain). After isolation from normal or zymosan inflamed rats, whole DRGs were immediately incubated with fluticasone (10nM) or vehicle (dimethyl sulfoxide) for 2 hours (in artificial cerebrospinal fluid bubbled with 95% oxygen and 5% carbon dioxide). The neurons in the whole DRG preparation were recorded with sharp microelectrodes after the incubation. Fluticasone decreased excitability of A cells (presumed myelinated cells, with action potential width <1.5 msec) from inflamed DRGs: fluticasone decreased the percentage of cells with the spontaneous activity, increased the action potential threshold voltage, and decreased the maximum number of action potentials that could be evoked with supra-threshold current injections. However, fluticasone did not affect the excitability of A cells from the normal DRGs. In addition, fluticasone did not affect the excitability of C (unmyelinated) cells from either normal or zymosan inflamed DRGs. Previous work showed that it is the A cells that become hyperexcitable in this model and reducing this hyperexcitability with various methods improved pain behaviors. Our study showed that fluticasone decreased the excitability of these cells in the zymosan inflamed DRG and might be a promising steroid for low back pain patients. This correlates well with our previous behavioral studies showing that locally applied fluticasone effectively reduces pain behaviors in this model, and suggests that some of these behavioral effects may be due to effects on neuronal hyperexcitability. Certain more typical steroid anti-inflammatory effects, such as regulating trafficking of immune cells from the blood into the DRG, could not occur in our isolated DRG preparation.

Disclosures: **X. Gong:** None. **Z. Song:** None. **J. Strong:** None. **J. Zhang:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: NIH AR068989

NIH NS055860

Title: Unexpected interactions between the mineralocorticoid and glucocorticoid receptors in a rat model of inflammatory low back pain

Authors: *S. IBRAHIM, W. XIE, J. A. STRONG, T. BERTA, J.-M. ZHANG
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Abstract: Low back pain is a major health problem. Inflammation of lumbar intervertebral discs and compression of nerve roots cause low back pain. Epidural steroid injections (ESI) are widely used in these conditions, but they are ineffective in many cases. Mineralocorticoid receptor (MR) activation has a critical role in the initiation of immune and inflammatory responses in the dorsal root ganglia (DRG). Steroids used clinically for ESI activate the target glucocorticoid receptor (GR) but also the MR. We hypothesize that this reduces effectiveness of currently used ESI. In this study, we used the local inflammation of the DRG (LID) model of inflammatory low back pain. The immune activator zymosan was applied in the vicinity of the L5 DRG, evoking mechanical and cold allodynia in the hind paw. We examined the effectiveness of a clinically used steroid, dexamethasone (Dexa) (a GR and MR agonist) with and without the MR antagonist Eplerenone (EPL), applied locally to the DRG. Although Dexa alone reduced pain behaviors, the effectiveness was improved when combined with EPL. A separate experiment comparing EPL alone to EPL plus Dexa confirmed that EPL potentiated the effects of Dexa: although EPL alone reduced pain behaviors, the combined therapy was more effective and had a more sustained action in ameliorating pain behaviors.
Using immunohistochemistry, we examined GR immunoreactivity in normal and inflamed DRG at different time points as well as in two treatment groups: Dexa with and without EPL. The GR signals was widely distributed in the nuclei of most neuronal and non-neuronal cells in the DRG prior to inflammatory challenge. However, GR signals begin to decrease on postoperative day 1 (POD1), and continued to decrease on POD7. At POD14, overall levels recovered, but GR immunoreactivity seemed to be higher in non-neuronal cells and lower in neuronal cells compared to normal DRG. In addition, the GR signal was unexpectedly enhanced in the DRG when EPL was combined with Dexa. Adding the EPL rescued the reduction of the GR signals compared to the single Dexa treatment.
Quantitative real-time RT-PCR showed that the mRNA expression level for GR was enhanced in

the LID on POD1 compared to the normal, while it was unchanged for MR. This suggests that reduction of GR immunoreactivity after DRG inflammation does not occur at the transcriptional level.
The overall ineffectiveness of the ESI may be due not only to activation of the pro-inflammatory MR, but also to the reduced signal level of GR in the inflamed sensory ganglia and unexpected interactions between GR and MR. This suggests that the combination therapy of EPL with Dexa may be more beneficial than Dexa alone in the management of low back pain.

Disclosures: S. Ibrahim: None. **W. Xie:** None. **J.A. Strong:** None. **T. Berta:** None. **J. Zhang:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant R01 DK066112S1

NIH Grant MAPP U01 DK82342

Title: Acyloxyacyl hydrolase modulates arachidonic acid metabolism and pain

Authors: *W. YANG[1], R. E. YAGGIE[1], M. JIANG[2], C. N. RUDICK[1], C. J. HECKMAN[2], A. J. SCHAEFFER[1], D. J. KLUMPP[1]
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Abstract: Phospholipids comprise cellular membranes but also act as reservoirs of releasable fatty acids that are metabolized into bioactive lipids. Arachidonic acid sequestration in phospholipids is a key step modulating production of eicosanoids that cause pain. Although detectable biochemically, the underlying arachidonic acid transacylases that mediate arachidonic acid movement between specific phospholipids have not been identified. Here, we show that acyloxyacyl hydrolase (AOAH), previously characterized as a leukocyte lipase that detoxifies bacterial lipopolysaccharide, mediates arachidonic acid homeostasis and pain modulation. AOAH expression along the bladder-brain axis is consistent with a role in bladder sensory function, and AOAH-deficient bladder pathology mimics that of pelvic pain patients. Homology with lecithin-cholesterol acyltransferase suggested that AOAH potentially mediates transfer of arachidonic acid between phospholipids. Spinal cord lipidomics revealed increased arachidonic acid-containing phosphatidylcholine in AOAH-deficient mice and concomitant decreased phosphatidylethanolamine. In spinal cords, AOAH deficiency was also associated with elevated arachidonic acid and PGE_2, and pelvic pain was reduced in AOAH-deficient mice by a PGE_2

receptor antagonist. Together, these findings suggest that AOAH modulates CNS pain pathways. Furthermore, the existence of AOAH variants raises the possibility that AOAH mediates other biochemical events involving diverse lipid substrates and biological processes.

Disclosures: W. Yang: None. **R.E. Yaggie:** None. **M. Jiang:** None. **C.N. Rudick:** None. **C.J. Heckman:** None. **A.J. Schaeffer:** None. **D.J. Klumpp:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.04/EE15

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI

Title: Expression of NLRP2 in the DRG and its regulation during inflammatory hyperalgesia

Authors: *Y. MATSUOKA[1], F. AMAYA[2]
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Abstract: Background
Nod like receptors (NLRs) regulate innate immune response and involve in the pathophysiology of neurodegenerative disease. NLRP2, one of the NLR family protein, is expressed in the astrocyte and involved in the neuroinflammation via caspase-1 activation. In the present study, we examined the expression of NLRP2 in the dorsal root ganglion (DRG) and investigated its regulation during the tissue inflammation induced pain hypersensitivity.
Method
Male C57BL/6 mice (20-25g) were used for the experiments. All experimental procedures were approved by the animal ethics committee of the Kyoto Prefectural University of Medicine. Tissue inflammation was produced by the intraplantar injection of complete Freund's adjuvant (CFA, 20μL) into the left hindpaw. Behavioral analysis including von Frey mechanical stimulation and hot plate testing were performed to confirm inflammation induced hyperalgesia. After the CFA injection, L4 and L5 DRG were removed and processed for the immunohistochemistry and real time PCR. Visualization of NLRP2 was performed using fluorescent immunohistochemistry using anti-NLRP2 antibody. Real time PCR was performed by using CYBR green master mixture kit with manufacturer's protocol. Caspase-1 activity was measured by using ELISA kit. Naive mice were used as control.
Result
Mechanical threshold and thermal withdrawal latency significantly reduced after the CFA treatment. In naive DRG, NLRP2 immunoreactivity was mainly detected in small-sized DRG

neurons. Signal intensity analysis revealed that NLRP2 immunoreactivity significantly increased 2days after the CFA injection. Real time PCR demonstrated that NLRP2 mRNA significantly increased in the CFA treated mice. Caspase-1 activity was significantly increased after the CFA injection.
Conclusion
Distinctive expression of NLRP2 within the small sized DRG neurons implicate a selective function of NLRP2 in the nociceptive transmission. Induction of NLRP2 in the DRG, together with increased caspase-1 activity, suggest that immune reaction in the peripheral nervous system contributes to the development of inflammatory hyperalgesia after the CFA treatment.

Disclosures: Y. Matsuoka: None. **F. Amaya:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.05/EE16

Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI

Title: Endogenous cannabinoids contribute to the resolution of incisional pain

Authors: H. TAKEMURA, M. MATSUDA, *F. AMAYA
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Abstract: Background
Endogenous cannabinoids effect on the peripheral nervous system and have anti-nociceptive function. Dysregulation of endogenous cannabinoids is associated with the development of chronic pain in clinical situation. We hypothesized that resolution of acute post-incisional pain requires endogenous cannabinoid anti-nociception. To clarify this, we investigated the expression level of endocannabinoid synthetic/degradation enzymes in the injured tissue during acute pain resolution phase. Pro-nociceptive effect of cannabinoid receptor 1 antagonist was also tested during this period.
Method
All experimental procedures were approved by the animal ethics committee of the Kyoto Prefectural University of Medicine. Plantar incision was made in left hindpaw of male Sprague-Dawley rats. Behavioral analysis for the withdrawal threshold against von Frey mechanical stimulation and withdrawal latency against radiant heat was performed up to 7 days after the surgery. Plantar tissue was removed and mRNA was extracted from left hindpaw 7 days after the incision. Expression level of NAPE-PLD, FAAH, DGL and MGL were determined by real time PCR. Naive rats were used as control. In other sets of experiments, AM251, cannabinoid

receptor 1 antagonist, was injected into left hindpaw 7days after the incision. Naive rats received intraplantar injection of AM251 were used as control. After AM251 injection, behavioral study was performed to determine mechanical threshold and thermal withdrawal latency.
Result
Mechanical threshold and thermal withdrawal latency immediately decreased after the incision, but returned to the baseline level 7days thereafter, demonstrating resolution of acute incisional pain. NAPE-PLD, FAAH, DGL and MGL mRNA expressions in the plantar tissue increased significantly 7days after the incision, compared to the naive control. Injection of AM251 reduced mechanical threshold in rats received plantar incision 7days before. Reduction of the mechanical threshold did not occur when AM251 was injected to naive control. Thermal withdrawal latency was not affected by the AM251 treatment.
Conclusion
Increased turnover of endogenous cannabinoids in the injured tissue participate pain resolution of acute post-incisional pain. Failure of pain resolution due to the dysregulation of endogenous cannabinoids might contribute to the pain chronicity after the surgery.

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Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.06/EE17

Topic: B.04. Ion Channels

Support: AR-059397

Title: Modulation of ASIC currents by opioid analgesics in rat sensory neurons

Authors: M. ZAREMBA, K. SEDEEK, *V. RUIZ-VELASCO
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Abstract: Acid-sensing ion channels (ASICs) are voltage-independent, H^+-gated ion channels that conduct primarily Na^+ ions and expressed in central and peripheral neurons. Dorsal root ganglion (DRG) neurons are known to express ASIC1 and ASIC3 subunit isoforms. ASIC3 isoforms exhibit biphasic current when exposed to an acidic external solution. The first component is rapidly inactivating and the second is a sustained current that persists as long as the pH remains low. Previously, we reported that the high affinity, endogenous mu opioid receptor (MOR) agonist, endomorphin-2 significantly potentiated ASIC3 sustained currents without MOR

stimulation. The purpose of the present study was to examine whether the potent analgesics oxycodone, fentanyl and remifentanil would modulate ASIC currents in acutely isolated rat DRG neurons, employing the whole-cell voltage-clamp technique. Exposure of DRG neurons to oxycodone (10 μm) or fentanyl (10 μm) or remifentanil (10 μm) in acidic solutions (pH 6.0) potentiated the sustained currents by 316±100% (n=6), 206±47% (n=8), and 137±49% (n=7), respectively, when compared to activation by pH 6.0 alone. On the other hand, the effect of the three MOR agonists on peak ASIC currents was variable (i.e. blocked, enhanced or no effect). These results suggest that, similar to endomorphins, clinically employed synthetic MOR agonists are capable of modulating ASICs in rat DRG neurons.

Disclosures: M. Zaremba: None. **K. Sedeek:** None. **V. Ruiz-Velasco:** None.

Poster

145. Pain Models: Pharmacology

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Topic: B.07. Synaptic Transmission

Support: The Anesthesia Research Fund of the New York University, Department of Anesthesiology (ERP)

CONACyT-SEP-México Grant No. 127658 (EMPA)

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Research Division of the Faculty of Medicine, UNAM

Title: Connexin 36 protein is expressed in lumbar dorsal rooth ganglia

Authors: *E. M. PEREZ-ARMENDARIZ[1], M. NORCINI[2], B. HERNÁNDEZ-TELLEZ[3], A. CASTELL-RODRÍGUEZ[3], C. CORONEL-CRUZ[3], A. SIDERIS[2], E. RECIO-PINTO[2]
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Abstract: The expression and cell distribution of connexin 36 (Cx36) was assessed in the adult rat lumbar dorsal root ganglia (DRG). Cx36 mRNA was detected in all lumbar DRG using qPCR. Cx36 protein was identified using immunohistochemistry (IHC) and immunofluorescence (IF) in lumbar DRG sections. Double IF studies showed co-labeling between anti-Cx36 and anti-β-III tubulin, a neuronal marker, and between anti-Cx36 and anti-glutamine synthetase, a satellite glial cell (SGC) marker. In neurons and fibers of all sizes an intense and uniform Cx36-IF

labeling was found with a higher density at the periphery than in the cytoplasm as detected with line scan analyses, supporting its expression at the membranes. These findings demonstrate that DRG neurons and SGCs express Cx36 and suggest that intercellular channels and/or hemichannels formed with this connexin may play a role in functional coordination between DRG cells.

Disclosures: E.M. Perez-armendariz: None. **M. Norcini:** None. **B. Hernández-Tellez:** None. **A. Castell-Rodríguez:** None. **C. Coronel-Cruz:** None. **A. Sideris:** None. **E. Recio-Pinto:** None.

Poster

145. Pain Models: Pharmacology

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Program#/Poster#: 145.08/EE19

Topic: D.03. Somatosensation: Pain

Support: A Grant-in-Aid for Scientific Research (C) (15K10566) from the Ministry of Education, Culture, Sports, Science and Technology, Japan

Title: Emotional dysfunction induced by social defeat stress lead to prolongation of postsurgical pain: A possible mechanism underlying GPR40/FFAR1

Authors: *F. AIZAWA, K. NAKAMOTO, S. TOKUYAMA
Dept. Clinic. Pharm., Sch. Pharmaceu. Sci., Kobegakuin Univ., Kobe, Japan

Abstract: *Aims;* Pain associated with various diseases is the most familiar with sensory and emotion. However, detailed mechanism underlying relationship between pain and emotion remains unclear. GPR40/FFAR1, one of the G-protein coupled receptor, is activated by middle to long chain free fatty acids including docosahexaenoic acids (DHA). Our previous studies have reported that several fatty acid including DHA and arachidonic acid are released by pain condition, suggesting that increased brain fatty acids involved in the regulation of endogenous pain control system. Furthermore, we found that brain DHA level immediately decreased after exposure of acute stress such as forced swimming. In the clinical study, n-3 fatty acids contents in the brain decreased in the patients with depression, and intakes of the n-3 fatty acids relieve psychiatry symptom. Based on our studies and previous reports, brain GPR40/FFAR1 could be closely related the regulation between pain and emotion. In the present study, we examined effect of GPR40/FFAR1 agonist on pain prolongation induced by the exposure of chronic emotional stress.
Materials and Methods; C57BL6J male mice received social defeat (SD) stress consecutive 10 days. Postsurgical pain was induced by a plantar incision in the right hind paw of mice. GW9508, a GPR40/FFAR1 agonist (0.1 mg/mL, 10 μL/mouse), or GW1100, a GPR40/FFAR1

antagonist (0.1 mg/mL, 10 μL/mouse), was intracerebroventricularly injected in mice at 7 days after incision. Mechanical hypersensitivity was evaluated by a von Frey filament test. Withdrawal response following hind paw stimulation was measured 10 times.
Results; Postsurgical pain lasted for 3 days, and return to base line levels on day 4 after surgery in the ipsilateral site of non-stress mice. On the other hand, SD stress mice caused mechanical hypersensitivity during 21 days after incision. Single treatment of GW9508 transiently suppressed the mechanical hyper sensitivity in SD stress mice at 7 days after incision. This effect was canceled by the pretreatment of GW1100.
Conclusion; Our findings suggest that the activation of brain GPR40/FFAR1 could be an important role the suppression of pain behavior associated with emotional dysfunction.

Disclosures: F. Aizawa: None. **K. Nakamoto:** None. **S. Tokuyama:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.09/EE20

Topic: D.03. Somatosensation: Pain

Support: CA196263

U54HL119893

Title: Peripherally restricted cannabinoid receptor agonist suppresses neuropathic pain symptoms in operant assays

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Abstract: Chronic pain of neuropathic origin is difficult to manage as the therapeutic window of current medications is limited by their undesirable side-effects. We recently developed a novel class of cannabinoid based analgesics with a high peripheral selectivity and demonstrated the anti-allodynic efficacy of one of the compounds, PrNMI (4-{2-[-(1E)-1[(4-propylnaphthalen-1-yl) methylidene]-1H-inden-3-yl] ethyl} morpholine) in rodent models of cancer pain and chemotherapy induced peripheral neuropathy (CIPN) using assays of withdrawal reflexes (Mulpuri et al, SFN Abstr. Vol. 41:146.25, 2016). However, a limitation of sensory reflex assays is that they don't address cerebral processing of pain which can be accomplished using complex operant based assays. Therefore, we tested the efficacy of PrNMI in suppression of neuropathy symptoms using two different operant conflict models: one involving positive and the other

negative reinforcement. In the negative reinforcement model, CIPN and control rats were given a choice either to remain in a brightly illuminated compartment or to escape to a dark compartment by crossing an array of height adjustable probes. In the positive reinforcement model, an orofacial operant assay with mechanical stimulation (Nitinol 0.009″ diameter) was used where trigeminal nerve injured and sham rats were given a choice either to receive a palatable reward or to avoid mechanical stimulation. CIPN treatment resulted in a significant increase in escape latency (~30 sec) to reach the dark compartment compared to their sham controls (~10 sec). Similarly, in an orofacial operant assay the reward consumption was significantly decreased in nerve injured rats (~55% of baseline) compared to sham controls (~90% of baseline) two weeks post-surgery. Pre-treatment with PrNMI (0.1 or 0.2 mg/kg, i.p.) decreased the escape latency to that of sham values while similar administration of vehicle had no effect on escape latencies. In an orofacial operant assay, pre-treatment with PrNMI, (0.3 mg.kg, i.p.) significantly increased reward consumption (~72% of baseline) compared to vehicle alone administrations (~48% of baseline) without any significant effect on sham reward consumption. Taken together, our results demonstrate that PrNMI can effectively suppress neuropathic pain symptoms in operant assays indicating a viable option for future clinical use.

Disclosures: Y. Mulpuri: None. **H.H. Seltzman:** None. **B.L. Schmidt:** None. **I. Spigelman:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.10/EE21

Topic: D.03. Somatosensation: Pain

Title: Development of a rat model of BDNF-induced neuropathic-like pain: a tool for drug discovery

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Abstract: Drug discovery in the field of neuropathic pain is a challenging area relying on the development of relevant preclinical models. Streptozocine-induced diabetes as well as sciatic nerve chronic constriction injury to the sciatic nerve (CCI-SN) are models of reference but required a sufficient period of time before occurrence of hyperalgesia and are associated with poor health conditions of animals. Previous studies have compared the direct effect of brain-derived nerve factor (BDNF) on pain mechanisms with neurobiological features of neuropathic pain induced by CCI-SN. In most of these works, an intrathecal administration of BDNF was performed under isoflurane anesthesia and was associated to mechanical hyperalgesia and/or

pain-related signaling pathways. However, it has been shown that isoflurane interacted with tropomyosin receptor kinase B signaling, a receptor of crucial importance in pain pathways suggesting a potential bias in the studies mentioned above. In the present study, we sought to develop a valuable and reliable preclinical tool to drug discovery in the field of neuropathic pain. The purpose was to induce a neuropathic-like pain associated with rapid development of hyperalgesia in the rat using intrathecal (it) BDNF administration without anesthesia.
BDNF (3 ng and 10 ng) or its vehicle were administered intrathecally in awake Sprague-Dawley rat using a method previously described. Pain threshold was measured using the Randall-Selitto paw-pressure test on days 3, 10, 14 and 17 to assess whether a single injection of BDNF was able to induce a sustainable mechanical hyperalgesia and to determine the optimal dose of BDNF. Afterwards the anti-hyperalgesic effects of pregabalin (30 mg/kg, ip) and morphine (3 mg/kg, sc) were assessed.
A rapid and sustainable decrease in the pressure threshold was observed from day 3 to day 17 after it administration of BDNF 3 ng compared to animals administered with vehicle (around -38%). Acute administration of morphine or pregabalin on day 3 and day 10 was able to reverse the BDNF-induced hyperalgesia. Moreover, no clinical sign was observed following the BDNF administration during the course of the experiments.
In line with previous studies, our data suggest that a single injection of BDNF is able to rapidly induce a sustainable mechanical hyperalgesia in the rat. The hyperalgesic outcome was reversed by morphine and pregabalin treatment supporting the validity and the robustness of this model. We propose this BDNF-induced hyperalgesia model as a valuable tool in a drug discovery perspective in the field of neuropathic pain.

Disclosures: C. Drieu La Rochelle: None. **D. Parachou:** None. **B. Le Gouriellec:** None. **M. Alix:** None. **S. Loiodice:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

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Program#/Poster#: 145.11/EE22

Topic: D.03. Somatosensation: Pain

Support: 2016M3A9B6021209

2015R1D1A1A01059208

brain pool

Title: The analgesic effects of sinomenine in peripharl nervous system: Involvement of inhibition of voltage-gated sodium channels

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Abstract: *Sinomenium acutum* has been used in traditional medicine to treat a painful disease such as rheumatic arthritis and neuralgia. Sinomenine, which is a main bioactive ingredient in *Sinomenium acutum,* has been reported to have an analgesic effect in diverse pain animal models. However little is known about the detailed mechanisms underlying peripheral analgesic effect of sinomenine. In the present study, we aimed to elucidate its cellular mechanism by using formalin-induced acute inflammatory pain model in mice. We found that intraperitoneal (i.p.) administration of sinomenine (50 mg/kg) suppressed formalin-induced paw licking behavior in both the first and the second phase. Formalin-induced c-Fos expression was also suppressed by sinomenine (50 mg/kg i.p.) in the superficial dorsal horn of spinal cord. When we examined the effect of sinomenine on small-sized dorsal root ganglion (DRG) neurons using whole cell patch clamp recordings, sinomenine reversibly increased threshold of single action potential and inhibited firing frequency of action potentials. Voltage-gated sodium channel currents (I_{Na}) were also significantly reduced by sinomenine in a dose-dependent manner (IC_{50} = 2.59 ± 0.4 mM). Finally, we confirmed that intraplantar (i.pl.) application of sinomenine suppressed formalin-induced pain behavior only in the first phase, but no the second phase. Taken together, our results suggest that sinomenine has a peripheral analgesic effect by inhibiting I_{Na}.

Disclosures: J. Lee: None. **S. Yoon:** None. **J. Won:** None. **H. Kim:** None. **Y. Kang:** None. **S. Oh:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.12/EE23

Topic: D.03. Somatosensation: Pain

Support: Hartman Foundation for Parkinson's Disease #64249

Title: Dopaminergic modulation of pain signaling in the dorsal horn of the spinal cord

Authors: *M. PUOPOLO[1], Y. LU[1], A. AZIM[2], K. YONGIL[2], M. REBECCHI[1]
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Abstract: Descending monoaminergic fibers from supraspinal centers powerfully modulate nociceptive signals in the dorsal horn of the spinal cord, making them an attractive target for new pharmacotherapies to treat pain. Hypothalamic A11 dopaminergic neurons are thought to provide the main source of spinal dopamine. The aim of this project was to investigate: 1) whether dopamine can modulate the synaptic transmission between primary nociceptors and lamina I projection neurons, and determine which dopamine receptors mediate the effects of dopamine; 2) whether ablation of A11 neurons can modulate pain signaling in vivo. For the in vitro studies, we used horizontal slices of the spinal cord form P16-P26 SD rats. Excitatory postsynaptic currents (EPSCs) were elicited by stimulation of L4 or L5 dorsal root and recorded from lamina I projection neurons using the patch clamp technique in whole-cell voltage clamp. The external solution was (in mM): 125 NaCl, 2.5 KCl, 1.25 $NaH_2PO_4.H_2O$, 26 $NaHCO_3$, 1 $MgCl_2$, 2 $CaCl_2$, 20 Glucose, 0.01 bicuculline, and 0.005 strychnine. The internal solution was (in mM): 125 $CsMeSO_3$, 10 NaCl, 2 $MgCl_2$, 10 HEPES, 10 EGTA, 4 MgATP, 0.3 NaGTP, 14 Phosphocreatine, 5 mM QX-314, pH=7.2. To ablate A11 dopaminergic neurons in vivo, 20 µg of 6-OHDA were injected into the right hypothalamic A11 nucleus. The threshold (g) for mechanical sensitivity was assessed with a von Frey anesthesiometer. Dopamine reduced the EPSC in a dose-dependent manner: 1 µM (35±22%, n=10); 3 µM (60±22%, n=12); 10 µM (69±20%, n=8); 20 µM (76±11%, n=8). 20 µM dopamine increased the paired pulse depression (PPD) ratio (second/first EPSC) from 0.44±0.17 to 0.79±0.25 (n=18), suggesting a presynaptic effect. The inhibitory effects of 3 and 10 µM dopamine on the EPSC were unchanged in the presence of 300 nM SCH 23390 (D1/D5 antagonist: 53±21%, n=6 and 65±22%, n=6, respectively). In contrast, the inhibitory effects of 3 µM dopamine on the EPSC were strongly reduced to 12±21% (n=13) in the presence of 1 µM U99194 (D3 antagonist). Lesion of A11 nucleus reduced the mechanical threshold by ~50% in the ipsilateral and ~23% in the contralateral hind paw. Immunohistochemistry confirmed that the ipsilateral A11 nucleus was completely ablated, while the contralateral A11 nucleus was unaffected. The data suggest that dopamine modulates the threshold for mechanical sensitivity in vivo by inhibiting the synaptic transmission between primary afferent fibers and lamina I projection neurons in the dorsal horn of the spinal cord. Pharmacological data in combination with analysis of the PPD ratio and dialysis of the postsynaptic neurons with GDP-beta-S support the presynaptic effect of dopamine mediated by D3 receptors.

Disclosures: M. Puopolo: None. **Y. Lu:** None. **A. Azim:** None. **K. Yongil:** None. **M. Rebecchi:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

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Title: Ketamine and norketamine reverse morphine tolerance more effectively than oxycodone tolerance: From behavior to drug availability

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Abstract: Background: Ketamine attenuates morphine tolerance by antagonizing NMDA receptors. However, a pharmacokinetic interaction between morphine and ketamine has also been studied. The interaction between oxycodone and ketamine has been only little addressed. We compared the effects of ketamine and norketamine in the reversal of morphine and oxycodone tolerance focusing on both pharmacodynamic and pharmacokinetic interactions.
Methods: Morphine (9.6 mg/day) or oxycodone (3.6 mg/day) was delivered to Sprague-Dawley rats by subcutaneous pumps. Once tolerance had developed, rats (n = 8–12 per treatment group) received subcutaneous injections of ketamine and norketamine. Tail flick, hot plate, and rotarod tests were performed. Drug concentrations were measured with high-performance liquid chromatography-tandem mass spectrometry.
Results: Antinociceptive tolerance to morphine and oxycodone developed similarly by day 6. Acute ketamine 10 mg/kg and norketamine 30 mg/kg attenuated morphine tolerance for 120 and 150 min, respectively, whereas in oxycodone-tolerant rats the effect lasted only 60 min. Both ketamine and norketamine increased the brain and serum concentrations of morphine and inhibited its metabolism to morphine-3-glucuronide, whereas oxycodone concentrations were not changed. Morphine, but not oxycodone, pretreatment increased brain and serum concentrations of ketamine and norketamine. Ketamine, but not norketamine, significantly impaired motor coordination.
Conclusions: Ketamine and norketamine reversed morphine tolerance more effectively than oxycodone tolerance, which may partly be explained by increased morphine concentrations after ketamine or norketamine administration. Norketamine may have a better therapeutic profile than ketamine in reversal of opioid tolerance. These results warrant pharmacokinetic studies in patients who are co-treated with ketamine and opioids.

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Poster

145. Pain Models: Pharmacology

Location: Halls A-C

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Program#/Poster#: 145.14/EE25

Topic: D.03. Somatosensation: Pain

Support: CONACYT 226454

CONACYT 256448

CNIC-R-2015-785-098

CYTED-RED CORNUCOPIA

CONACYT-610203

Title: Analgesic effects of Brasica oleracea var italica aqueous extracts form seeds, sprouts and vegetable

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Abstract: Pain is an enormous problem of health. It is associated with a wide range of injuries and diseases often caused by inflammation and it is sometimes the disease itself. . Because of the significant side effects of opioids, steroidal and non-steroidal anti-inflammatory medications, currently the most applied analgesics, there is a greater interest in natural alternatives, such as dietary supplements and herbal remedies, which have been used for centuries to reduce pain and inflammation, not only for mild to moderate aches but also for chronic pain. Broccoli sprouts (*Brassica olearacea* var. *italica)* are considered a rich source of health-promoting bioactive compounds related to the reduction of oxidative stress and inflammation such as glucosinolates, isothiocyanates, phenolic compounds, vitamins and minerals. In this study our aim was to explore the antinociceptive effects of a broccoli aqueous extract obtained from seeds, sprouts and vegetable using experimental models of pain and looking for a possible opioid mechanism. Mice (25-30 g) and rats (200-250 g) received via oral (p.o.) or intraperitoneal (i.p.) the extract and then they were submitted to the writhing and formalin tests, respectively. Gastric damage or sedative-like response, as adverse effects commonly observed in anti-inflammatory non-steroidal and opioid analgesic drug administration, respectively, were also explored. Antinociception, but not sedative or gastric injury response, was observed in a significant and dose-dependent manner

mainly in the sprouts aqueous extract (50-500 mg/kg, i.p. and 500-2000 mg/kg, p.o.) in comparison to the vehicle group. This effect was major in sprouts than in similar doses of seeds or vegetable aqueous extracts; these effects resembled those observed with the analgesic tramadol (30 mg/kg, i.p.) in writhing and formalin assessment. Blockage of opioid receptors by naloxone (1 mg/kg, i.p.) produced partial inhibition in the antinociceptive effect of the sprouts in both assays. In conclusion this study gives evidence of the potential activity of Broccoli as nutraceutical, especially as sprouts, for the pain therapy. Supported by CONACYT 226454 AND 256448, CNIC-R-2015-785-098 and CYTED-RED CORNUCOPIA grants, but also the scholarship CONACYT-610203.

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Poster

145. Pain Models: Pharmacology

Location: Halls A-C

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Topic: D.03. Somatosensation: Pain

Support: Indian Council of Medical Research (ICMR), New Delhi, India

Title: Intrathecal administration of arachidonylcyclopropylamide, a cannabinoid type 1 receptor agonist attenuates postoperative pain in rats

Authors: *M. GAUTAM[1], S. GUPTA[2], R. KUMAR[2], P. PRASOON[2], S. B. RAY[2]
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Abstract: Background: The endocannabinoid system which includes endogenously synthesized cannabinoids like anandamide, cannabinoid receptors (type 1 & 2) and enzymes associated with their synthesis and breakdown contributes towards maintaining a basal antinociceptive tone in rodents. Besides, systemic administration of cannabinoid drugs produces a distinct antinociceptive effect. However, these also produce psychomotor alterations. One of the options for avoiding the side effects is to selectively activate the cannabinoid receptors (CBr) in the spinal cord. In the present study, we evaluated the antinociceptive effect of arachidonylcyclopropylamide (ACPA), a specific type 1 CBr agonist, after direct intrathecal administration.
Materials and methods: Sprague-Dawley rats were subjected to hind paw incision following preemptive one-time intrathecal administration of 1, 3 or 10 µg ACPA. The antinociceptive effect was compared to morphine (10 µg). The antinociceptive effect of ACPA was tested for reversibility. Motor coordination was examined by rotarod apparatus. Spinal CB1r expression was observed by immunohistochemistry. Finally, both ACPA and morphine (10 µg each) were

co-administered intrathecally.
Results: Both ACPA (1, 3 or 10 µg) and morphine significantly decreased guarding behaviour and allodynia in comparison to control group. Thermal hyperalgesia was decreased by 3 µg ACPA only (2 h, 8h-day 5) in comparison to morphine (2 h). ACPA-induced antinociception was reversed by AM251. ACPA and morphine co-administration produced a synergistic interaction with a significant decrease in guarding, allodynia and hyperalgesia in the initial hours after incision. Immunohistochemistry showed CB1r expression in the superficial part of the dorsal horn. Rotarod findings did not show any significant alteration in the motor coordination.
Conclusion: ACPA likely activated CB1 receptors in the spinal cord to produce the antinociceptive effect. Further studies are required in this direction.

Disclosures: M. Gautam: None. **S. Gupta:** None. **R. Kumar:** None. **P. Prasoon:** None. **S.B. Ray:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: JSPS KAKENHI Grant 26460112

Title: Involvement of $Ca_v3.2$ T-type calcium channels in zinc deficiency-induced mechanical allodynia in mice

Authors: *F. SEKIGUCHI, S. TOMITA, S. SHIKIMI, M. TSUBOTA, A. KAWABATA
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Abstract: Zinc, an essential trace element, binds to various proteins and modifies their function. $Ca_v3.2$ T-type calcium channels (T-channels) are abundantly expressed in sensory neurons and play a role in the development of inflammatory and neuropathic pain. In physiological conditions, the function of $Ca_v3.2$ is suppressed by extracellular Zn^{2+} that binds to the 191st histidine residue in the channel molecule (Sekiguchi & Kawabata, J Pharmacol Sci 122, 244, 2013). Exogenously applied zinc chelator, L-cysteine or hydrogen sulfide enhances $Ca_v3.2$ function and promotes somatic and visceral pain (Nelson et al., J Neurosci 27, 8250, 2007; Maeda et al., Pain 142, 127, 2009; Matsunami et al., Neuroscience 181, 257, 2011; Sekiguchi et al., Biochem Biophys Res Commun 445, 225, 2014). We thus examined effects of zinc deficiency on somatic pain sensitivity in mice. Mice were fed with Zinc-deficient diet [Zn(-)] or the control diet [Zn(+)]. Zinc levels in the plasma and hindpaw tissue were measured by ICP-MS. Mechanical nociceptive threshold was assessed in the hindpaw by von Frey test. Protein levels in the dorsal root ganglia (DRG) and hindpaw of mice were determined by Western

blotting. The Zn(-)-fed mice exhibited the decreased plasma zinc levels but increased zinc content in the hindpaw, as compared with the Zn(+)-fed mice. Protein levels of ZIP6, a transporter for zinc uptake, in the hindpaw was upregulated in Zn(-)-mice. Nociceptive threshold significantly decreased on day 4 and reached the bottom on day 8 after the onset of the feeding with Zn(-). The Zn(-)-induced allodynia was completely blocked by a T-channel blocker or $Ca_v3.2$ knockdown in the sensory neurons, and was not promoted by intraplantar administration of NaHS, a hydrogen sulfide donor, known to enhance $Ca_v3.2$ activity via interaction with zinc. Similarly, intraplantar administration of N,N,N',N'-tetrakis(2-pyridylmethyl)ethylenediamine (TPEN), a zinc chelator, produced long-lasting allodynia, which was partially restored by T-channel blockers. Protein levels of $Ca_v3.2$ in DRG did not significantly increase in Zn(-)-mice. Together, chronic and acute zinc deficiency appears to enhance $Ca_v3.2$ activity, leading to sensitization of sensory neurons and acceleration of pain signals.

Disclosures: F. Sekiguchi: None. **S. Tomita:** None. **S. Shikimi:** None. **M. Tsubota:** None. **A. Kawabata:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: NIDA Grant DA041229

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Harlan Scholars Research Program

Title: The cannabinoid CB_2 agonist GW405833 suppresses inflammatory and neuropathic pain through a CB_1 mechanism that is independent of CB_2 receptors in mice

Authors: *A. LI[1], L. M. CAREY, IV[1,2], K. MACKIE[1,2,3], A. G. HOHMANN[1,2,3]
[1]Psychological and Brain Sci., [2]Program in Neurosci., [3]Gill Ctr. for Biomolecular Sci., Indiana Univ., Bloomington, IN

Abstract: GW405833, widely accepted as a cannabinoid CB_2 agonist, suppresses pathological pain in preclinical models without unwanted central side effects of CB_1 agonists. However, recent *in vitro* studies suggest that GW405833 may also behave as a non-competitive CB_1

antagonist (Dhopeshwarkhar et al. (2017) JPET 360:300-311), suggesting that its pharmacology is more complex than initially appreciated. Here, we further investigated the pharmacological specificity of *in vivo* antinociceptive actions of GW405833 in models of neuropathic (i.e. partial sciatic nerve ligation (PSNL) model) and inflammatory (i.e. complete Freund's adjuvant (CFA) model) pain using CB_2 and CB_1 knockout (KO) mice, their respective wild-type (WT) mice and both CB_2 and CB_1 antagonists. GW405833 (3, 10, and 30 mg/kg i.p.) dose-dependently reversed established mechanical allodynia in both pain models in WT mice. However, the anti-allodynic effects of GW405833 were fully preserved in CB_2KO mice and absent in CB_1KO mice. Furthermore, anti-allodynic efficacy of GW405833 (30 mg/kg i.p.) was completely blocked by the CB_1 antagonist SR141716A (10 mg/kg i.p.) but not by the CB_2 antagonist SR144528 (10 mg/kg i.p.). Thus, the antinociceptive properties of GW405833 are dependent upon CB_1 receptors. GW405833 (30 mg/kg i.p.) was also inactive in a tetrad of tests measuring cardinal signs of CB_1 activation. Additionally, unlike SR141716A (10 mg/kg i.p.), GW405833 (10 mg/kg, i.p.) did not act as a CB_1 antagonist *in vivo* to precipitate withdrawal in mice treated chronically with Δ^9-tetrahydrocannabinol. The present results suggest that anti-allodynic efficacy of GW405833 is CB_1-dependent but does not involve engagement of the CB_1 receptor's orthosteric site.

Disclosures: **A. Li:** None. **L.M. Carey:** None. **K. Mackie:** None. **A.G. Hohmann:** None.

Poster

145. Pain Models: Pharmacology

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Program#/Poster#: 145.18/EE29

Topic: D.03. Somatosensation: Pain

Title: Natural medicines and pain: Effects of methanolic extract of Corni fructus in rat

Authors: *T. T. JOHNSON[1], B. J. LINN[1], J. E. MEYERS-MANOR[1], R. BRISBOIS[2], E. P. WIERTELAK[1]
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Abstract: The adverse side effects and potential for dependency associated with opioid analgesics provide ample motivation for examination of potential alternative solutions for the control of pain and suffering. Mechanisms commonly targeted by antinociceptive agents frequently entail interactions between opioid and dopaminergic (D2) receptors. Anti-inflammatory action is thought to be prompted by agonizing G protein-coupled receptors, among them, peroxisome proliferator-activated receptors, such as through the inhibition of chemokines, cyclooxygenase-2, and nitric oxide synthase. Our study investigated the antinociceptive properties of Corni fructus, the fruit of Cornus officinalis, which is utilized for pain relief in a variety of traditional medical practices. Soxhlet extraction with 90% methanol solvent produced

an extract of 1.615 (mg/mL) and was diluted in a 1:1 fashion with saline. In study 1, subjects (rats; Sprague Dawley) received 0.1 mL/kg extract or equivolume saline via subcutaneous administration. One half hour after administration, nociceptive sensitivity was assessed using the formalin assay. Results revealed reduction of pain-related behaviors across all time points in the formalin test for subjects receiving extract. Study 2 utilized the same injection protocol, but employed the tail-flick assay, which revealed a marginally significant effect of the extract. In study 3, dose response effects were examined using a gavage administration, with dose volumes ranging from 1 mL to 10 mL versus water controls. Results revealed significant and incremental effects on pain behaviors with each increased dosage in the formalin assay. These results illustrate Corni fructus' potential as a pain-relieving agent, and moreover, suggest that this natural medicine may provide an alternative for opioid analgesics in some applications. Future research should investigate the mechanisms by which Corni fructus exerts these effects in order to better assess the suitability of this substance as a novel approach for the control of pain and suffering in humans.

Disclosures: **T.T. Johnson:** None. **B.J. Linn:** None. **J.E. Meyers-Manor:** None. **R. Brisbois:** None. **E.P. Wiertelak:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 145.19/FF1

Topic: D.03. Somatosensation: Pain

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CNPq/MS/SCTIE/DECIT #466805/2014-4

Title: Cannabidiol is a potential therapeutic for the affective-motivational dimension of pain in rats

Authors: *K. GENARO[1], D. FABRIS[2], A. F. ARANTES[3], A. W. ZUARDI[2], J. S. CRIPPA[2], W. A. PRADO[4]
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Abstract: Pain involves different brain regions and is critically determined by emotional processing. Among other areas, the rostral anterior cingulate cortex (rACC) is implicated in the

processing of affective pain. Drugs that interfere with the endocannabinoid system are alternatives for the management of clinical pain. Cannabidiol (CBD), a phytocannabinoid found in *Cannabis sativa*, has been utilized in preclinical and clinical studies for the treatment of pain. Herein, we evaluate the effects of CBD, injected either systemically or locally into the rACC, on mechanical allodynia in a postoperative pain model and on the negative reinforcement produced by relief of spontaneous incision pain. Additionally, we explored whether CBD underlies the reward of pain relief after systemic or rACC injection. Male Wistar rats were submitted to a model of incision pain. All rats had mechanical allodynia, which was less intense after intraperitoneal CBD (3 and 10 mg/kg). Conditioned place preference (CPP) paradigm was used to assess negative reinforcement. Intraperitoneal CBD (1 and 3 mg/kg) inverted the CPP produced by peripheral nerve block even at doses that do not change mechanical allodynia. CBD (10 to 40 nmol/0.25 µL) injected into the rACC reduced mechanical allodynia in a dose-dependent manner. CBD (5 nmol/0.25 µL) did not change mechanical allodynia, but reduced peripheral nerve block-induced CPP, and the higher doses inverted the CPP. Additionally, CBD injected systemically or into the rACC at doses that did not change the incision pain evoked by mechanical stimulation significantly produced CPP by itself. Therefore, a non-rewarding dose of CBD in sham-incised rats becomes rewarding in incised rats, presumably because of pain relief or reduction of pain aversiveness. The study provides evidence that CBD influences different dimensions of the response of rats to a surgical incision, and the results establish the rACC as a brain area from which CBD evokes antinociceptive effects in a manner similar to the systemic administration of CBD. In addition, the study gives further support to the notion that the sensorial and affective dimensions of pain may be differentially modulated by CBD.

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Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: United States Fulbright Foundation

Title: Effects of alpha7nicotinic acetylcholine receptor positive allosteric modulator on microglial brain-derived neurotrophic factor expression in lipopolysaccharide-induced neuroinflammatory pain in mice

Authors: *S. RAHMAN, M. ABBAS
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Abstract: We have shown that 3a,4,5,9b-tetrahydro-4-(1-naphthalenyl)-3*H*-cyclopentan[*c*]quinoline-8-sulfonamide (TQS), α7 nicotinic acetylcholine receptor (nAChR) positive allosteric modulator (PAM), reduces neuroinflammatory pain by decreasing microglial activation in the hippocampus. It remains unknown whether microglial activation associated brain-derived neurotrophic factor (BDNF) expression in the hippocampus is involved in neuroinflammatory pain. The objective of the present study was to determine the effects of TQS on BDNF expression following lipopolysaccharide (LPS)-induced neuroinflammatory pain in hippocampus. Pretreatment of TQS (1 or 4 mg/kg, i.p.) reduced LPS-induced increased BDNF mRNA expression in the hippocampus and the effects of TQS were reversed by methyllycaconitine (3 mg/kg), an α7 nAChR antagonist. Moreover, TQS decreased LPS-induced increased BDNF immunofluorescence in the dentate gyrus and CA1 region of the hippocampus. In addition, administration of ANA-12 (0.25 or 0.5 mg/kg), a tyrosine receptor kinase B/BDNF receptor antagonist, significantly reduced LPS-induced tactile allodynia and thermal hyperalgesia. Taken together, these results suggest that TQS decreases LPS-induced neuroinflammatory pain by reducing microglial BDNF expression in the hippocampus by targeting microglial α7 nAChR. Therefore, α7 nAChR PAM such as TQS could be a potential drug candidate for the treatment of neuroinflammatory pain. (*Supported in part by US Fulbright Foundation).*

Disclosures: S. Rahman: None. **M. Abbas:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: JUST/Deanship of Research

Title: Sucrose inhibited hyperalgesia, induced by injection of CFA in hind paws of rat pups, during infancy and adulthood

Authors: *K. NUSEIR[1], A. ALTARIFI[2], A. TASSALQ[3]
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Abstract: Premature infants are usually subjected to multiple painful and invasive procedures in the neonatal intensive care unit (NICU) during the first days of their lives. Early painful procedure experiences during this critical period of neurodevelopment, have been associated with short and long-term consequences. These painful procedures are inadequately managed in these patients group due to difficulties in pain assessment and management, along with fear of adverse effect from analgesics.Several randomized control trials have shown that oral intake of

sucrose, causes analgesia by its effectiveness on physiological and behavioral signals of pain as well as reducing pain score in preterm and term neonates and its long-term consequences.In this study we examined, using rat pups model, the hypothesis that injection of inflammatory agent during infancy will alter pain sensitivity and tolerability during infancy and adulthood, and oral intake of sucrose solution will prevent inflammatory pain-induced sensitivity and tolerability impairments through its analgesic effect. Sucrose was compared to ibuprofen, a non-steroidal anti-inflammatory drug commonly used during infancy. Rat pups were either injected with Complete Freund's Adjuvant (CFA), an inflammatory agent, in both hind paws, or with saline for the control group. CFA groups were treated with either ibuprofen or sucrose. All treatments started on day five of birth and continued until day ten. Pain threshold via foot-withdrawal latency (FWL) to hot plate and Von Frey was measured from day six till day ten then on day fourteen, day twenty-eight, and day fifty-six. At the end of behavioral tests animals were killed, blood was collected, and the hippocampus was dissected. Levels of β-endorphin and enkephalin in the serum will be measured, while brain derived neurotropic factor (BDNF) levels in the hippocampus will be assessed using ELISA.
Results of behavioral studies showed that CFA injected in rat paws caused hypersensitivity to pain that persisted through adulthood. While ibuprofen and oral sucrose significantly decreased pain sensitivity and tolerability and increased pain threshold. Interestingly, sucrose was more effective than ibuprofen in reversing pain hypersensitivity during infancy and adulthood.

Disclosures: K. Nuseir: None. **A. Altarifi:** None. **A. Tassalq:** None.

Poster

145. Pain Models: Pharmacology

Location: Halls A-C

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Program#/Poster#: 145.22/FF4

Topic: D.03. Somatosensation: Pain

Title: Questioning the morphine paradigm: Dose-related aggressive behavior in pigs

Authors: *S. B. MEILIN[1], I. SABBAG[2], D. CASTEL[3]
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Abstract: Introduction: Morphine has long been used for post-operative treatment in pigs undergoing surgical procedures. Reported dosages range from 0.2 mg/kg to a few mg/kg. We have previously shown that the analgesic effect of morphine at a dose lower than 1 mg/kg in skin incision operations is questionable (Castel et al., 2014). The PK data reported in the literature show that the T1/2 measured following an IV administration of 2.5 mg/kg was 1 hour in the plasma and 3.5 hours in the CSF. Back in 1992, a study conducted to test the analgesic effect of

morphine reported that it is effective for several hours, which correlates with the T1/2 found in the spinal cord. However, this study was problematic, since the motor activity of the animals was limited. Malavasi et al. (2005) used a comprehensive activity scoring method and videotaping of the animals for 60 hours post-abdominal surgery. These authors showed that there was no difference in the activity score versus the baseline prior to surgery following treatment with morphine and Fentanyl. They therefore concluded that morphine treatment together with Fentanyl was effective in reducing pain. However, the data presented in their study lacks an objective follow-up on animal behavior following morphine treatment. Methods: Pigs (male 15-20 kg) were treated with different doses of morphine. Half an hour later, the animals were placed in an open field and their locomotor function was monitored using a camera and the AnyMaze data acquisition and analysis software. All changes in their behavior were also recorded. Results: The animals exhibited a significant and dose-related increase in walking distance. Furthermore, their walking pattern changed. Prior to treatment with morphine, the animals walked around the entire area, without any specific preference. Half an hour after treatment, the animals walked mainly near the door entrance. They exhibited aggressive behavior, including banging on the entrance door to the open field. When placed back in their home-pen, the pigs were observed biting each others' tails. This behavior was dose-related. Additionally, none of the animals defecated during the open field test (5 to 30 min). This phenomenon was not dose-related. Conclusions: We have previously found that morphine doses lower than 1 mg/kg for relief of simple, moderate incision pain are questionable. However, the present study suggests that higher doses of morphine result in significant side effects. This finding undermines the current morphine treatment paradigm for post-surgery pain relief in pigs of this age, strain and gender.

Disclosures: S.B. Meilin: None. **I. Sabbag:** None. **D. Castel:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Title: A dose response study on the effect of prostaglandin E2 on thermal nociceptive sensitivity

Authors: *A. F. DOMENICHIELLO[1,2], B. C. WILHITE[3], G. S. KEYES[2], C. E. RAMSDEN[2]
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Abstract: The inhibition of prostaglandin (PG) biosynthesis has been used to treat chronic pain for thousands of years. Today non-steroidal anti-inflammatory drugs (which largely inhibit prostaglandin synthesis) are widely used to treat acute and chronic pain. Four main types of prostaglandins (PGD2, PGE2, PGF2 and PGI2) are synthesized from arachidonic acid during

inflammation and have been demonstrated to impact nociception. PGE2 has been most studied and utilized for its pain producing properties. PGE2 has been demonstrated to increase hypersensitivity in rodent nociceptive behavioral models when applied centrally and/or peripherally. Surprisingly, there are no published reports that use withdrawal from radiant light beam (Hargreaves method) to examine the dose response effect of peripherally applied PGE2 on thermal nociceptive hypersensitivity. To address this gap in the literature, we performed a dose response study examining the effects of PGE2, injected intradermally into the hindpaw, on thermal nociceptive hypersensitivity. The procedure for the behavioral assessments were as follows. For one week prior to behavioral testing rats were habituated to testing conditions. On testing days rats were anesthetized with sevoflurane and injected, intradermally with PGE2 (30, 3, 0.3, 0.03 or 0 μg/rat $n \geq 10$) into the plantar surface of the hindpaw. Once the animal recovered from anesthesia (<30min post injection), thermal hypersensitivity was assessed by measuring withdrawal latency from a radiant light stimulus. The primary outcome was to determine the dose of PGE2 causing the most pronounced increase in thermal hypersensitivity. A secondary objective, was to determine the minimum dose of PGE2 required to cause statistically significant decreases in thermal withdrawal latency as compared to rats injected with vehicle. We found that all rats injected with PGE2 had lower withdrawal latencies as compared to rats injected with vehicle, with the 30 μg dose of PGE2 producing the most pronounced thermal nociceptive hypersensitivity (lowest thermal withdrawal latencies). This work fills an evidence gap and provides context to guide dose selection in future rodent pain behavior studies.

Disclosures: A.F. Domenichiello: None. **B.C. Wilhite:** None. **G.S. Keyes:** None. **C.E. Ramsden:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

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Title: Inhibition of 12-lipoxygenase in spinal glia attenuates TLR4-dependent, NSAID-insensitive inflammatory hyperalgesia

Authors: *A. GREGUS[1], M. W. BUCZYNSKI[1], B. FITZSIMMONS[2], C. I. SVENSSON[3], Q. XU[4], E. DENNIS[5], T. L. YAKSH[6]
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Abstract: Previously, we demonstrated that increased synthesis of arachidonic acid (AA)-derived metabolites of spinal 12-lipoxygenases (12-LOX), in particular the hepoxilins (HXA_3 and HXB_3) and 12-HETE, contributes to hyperalgesia following peripheral inflammation with intraplantar carrageenan. In addition, we and others have shown that spinal delivery of agonists of Toll-like receptor 4 (TLR4), such as LPS and $(Kdo)_2$-Lipid A (the active component of LPS), elicits tactile allodynia in rats. After tissue inflammation or injury, non-neuronal cells (particularly astrocytes and microglia) contribute to these nociceptive cascades at the spinal level via stimulation by a variety of mediators including glutamate, substance P, ATP, cytokines or chemokines as well as ligands of TLR. While it is widely accepted that activation of TLR4 by its ligand LPS releases eicosanoids from cyclooxygenase (COX) and/or 5-lipoxygenase (5-LOX) pathways, the upstream activators as well as the cellular source(s) of 12-LOX metabolites during inflammation remain largely undefined. Surprisingly, intrathecal (IT) administration of nonsteroidal inflammatory drugs (NSAIDs) such as ibuprofen and ketorolac failed to attenuate this hyperesthesia despite attenuation of TLR4-induced spinal PGE_2 release. In the current study, we demonstrate in rats that direct activation of spinal TLR4 releases 12-LOX metabolites *in vivo* as well as in cultured glia but not in neurons, and that IT delivery of selective, potent inhibitors of human *Alox15* also target the rat homolog and prevent the ensuing NSAID-insensitive hyperpathic state.

Disclosures: A. Gregus: None. **M.W. Buczynski:** None. **B. Fitzsimmons:** None. **C.I. Svensson:** None. **Q. Xu:** None. **E. Dennis:** None. **T.L. Yaksh:** None.

Poster

145. Pain Models: Pharmacology

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Program#/Poster#: 145.25/FF7

Topic: D.03. Somatosensation: Pain

Title: Baclofen and opioid synergism in mice: New insights and potential treatments

Authors: S. K. TOTSCH, R. Y. MEIR, A. R. LANDIS, T. L. QUINN, *R. E. SORGE
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Abstract: There is a desperate need for opioid analgesic options for chronic pain to address the recent recommendations of the CDC and FDA aimed at reducing prescription opioid use/abuse.

Unfortunately, there are few alternatives for moderate to severe chronic pain aside from opioid drugs. Therefore multimodal therapies may be the answer. The overlapping expression of GABA and opioid receptors in the central nervous system suggests that the two systems are likely interrelated and may modify one another. The GABA B receptor agonist baclofen has been used as a treatment for spasticity and addiction, but there is evidence supporting its potential as a weak analgesic. We have been interested in the interaction between baclofen and opioid analgesics with respect to analgesic efficacy and abuse potential. Analgesic interactions were assessed in the hot plate test, whereas rewarding interactions were assessed via the conditioned place preference procedure with outbred CD1 mice. To date, we have tested the interactions between baclofen and the opioids morphine, oxycodone, buprenorphine, methadone and fentanyl using isobolographic analyses. All opioids tested with baclofen show synergism in analgesia and no significant interactions in place conditioning. This effect is also consistent in another common strain of mice (C57BL/6J) and in rats. In tests of tolerance, the combination of baclofen and morphine, given repeatedly, showed less tolerance and constipation than an equipotent dose of morphine alone. Baclofen and morphine also show interactive analgesic effects when tested in chronic pain. Finally, acute administration of baclofen reduced the self-administration of morphine, suggesting a reward-reducing effect. Together these data support the use of baclofen coupled with opioids to enhance analgesia while reducing the abuse liability and associated side effects of opioid drugs.

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Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: DFG

Title: Alpha2/alpha3 $GABA_A$ receptor subtype-selective benzodiazepines reduce not only hyperalgesia but also the aversive component of on-going neuropathic pain

Authors: *E. NEUMANN[1], H. U. ZEILHOFER[1,2]
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Abstract: GABAA receptors (GABAARs) play a key role in spinal control of nociception and pain. Diminished $GABA_AR$-mediated inhibition in the spinal dorsal horn is a major contributor to chronic pain states. Experiments in $GABA_AR$ point mutated mice and with several α2/α3

GABAAR preferring compounds have shown that positive allosteric modulation of spinal GABAARs containing the α2 and/or α3 subunit alleviates hyperalgesia in rodent models of chronic neuropathic and inflammatory pain. TPA023B is a GABAAR modulator that combines high selectivity for α2/α3 GABAARs with favorable pharmacokinetics in mice. TPA023B is completely devoid of sedation and motor impairment in mice but has not yet been tested in pain models. In the present study, we investigated TPA023B in classical (withdrawal readout based) pain tests and in addition in operant learning paradigms such as conditioned place preference. TPA023B significantly reduced mechanical hyperalgesia assessed with von Frey filaments in C57BL/6 mice after systemic application. In the conditioned place preference test, TPA023B administered intrathecally at a dose of 0.3 mg/kg did not induce place preference in naïve mice. However, in neuropathic mice that had undergone chronic constriction injury surgery 7 days before testing, TPA023B induced a pronounced preference for the drug-paired chamber. Our data indicate that subtype-selective α2/α3 $GABA_AR$ agonists do not only reduce hyperalgesia but also the aversive component of on-going neuropathic pain.

Disclosures: E. Neumann: None. **H.U. Zeilhofer:** None.

Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Support: NIH Grant DA037355

Title: Tolerance to WIN55,212-2 but not CP55,940 is prevented in mice expressing a 'desensitization-resistant' form of the CB_1 receptor

Authors: *C. M. NEALON[1], D. HALE[1], A. N. HENDERSON-REDMOND[1], M. B. YUILL[1], D. J. MORGAN[1,2]
[1]Anesthesiol. and Perioperative Med., [2]Pharmacol., Penn State Col. of Med., Hershey, PA

Abstract: The focus of this study was to investigate whether classical G protein-coupled receptor kinase (GRK)- and βarrestin2-mediated receptor desensitization is required for antinociceptive tolerance to WIN55,212-2 or CP55,940, both synthetic, high potency cannabinoid agonists. We used S426A/S430A mutant mice expressing a 'desensitization-resistant' form of cannabinoid receptor 1 (CB_1) to investigate the essential role of this mechanism in tolerance to WIN55,212-2. We have previously demonstrated that antinociceptive tolerance to Δ^9-THC is mediated in part by this mechanism. Antinociceptive tolerance to repeated daily administration of WIN55,212-2 and CP55,940 was assessed in wild-type and S426A/S430A mice using tests of thermal (hot plate, tail flick), inflammatory (formalin) and

chemotherapy-evoked neuropathic (cisplatin) pain. We found that antinociceptive tolerance to WIN55,212-2 was profoundly delayed in the desensitization-resistant mice compared to wild-type littermate controls. Interestingly, this genotype difference was not observed in tolerance to the hypothermic or cataleptic effects of WIN55,212-2. We found that tolerance to the antinociceptive effects of CP55,940 was slower to develop in wild-type mice compared to WIN55,212-2. Interestingly, tolerance to antinociceptive effects of CP55,940 was only modestly delayed in S426A/S430A mutant mice compared to wild-type controls. These findings suggest that GRK- and βarrestin2-mediated desensitization of CB_1 may be the predominant mechanism responsible for antinociceptive tolerance to WIN55,212-2, but only plays a small role in tolerance to CP55,940. This finding suggests the possibility of agonist-specific mechanisms cannabinoid tolerance.

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Poster

145. Pain Models: Pharmacology

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Topic: D.03. Somatosensation: Pain

Title: Analgesics assessment in rat MIA model using the Bioseb automated dynamic weight bearing system

Authors: H. RASHID, *J. DOUVILLE, R. SAMADFAM
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Abstract: The rat monoiodo acetate (MIA)-induced osteoarthritic (OA) joint pain model is recognized as one of the most translatable joint pain models. Weight bearing assessment has been extensively used to measure joint pain in this model. In this study, we compare effects of various analgesics in this model using the BioSeb dynamic weight bearing assessment system (DWB). Monoarthritic joint pain is induced in rat by a single intra-articular injection of MIA (3mg/25uL, Day 1) into the right hind knee joint. Weight bearing pattern in the rats is then assessed by the Bioseb's DWB system. The system consists of an arena box with a pressure-sensitive sensor mat on the bottom and an attached high-resolution camera on the top. The rat can move freely inside the arena box. The system automatically calculates the weight borne by each limb and the tail. Joint pain in the rat is indicated by a reduction in weight bearing by the MIA-injected right hind limb. Effects of analgesics tramadol, morphine, dexamethasone, naproxen and celecoxib on MIA-induced joint pain were evaluated after a single dosing as well as after dosing for 3-4 days with the analgesics. Weight bearing assessments were performed at various time points following MIA injection. As expected, injection of MIA into the right hind

knee joint caused a reduction in weight bearing by the ipsilateral limb indicating joint pain. The deficit in weight bearing by the MIA-injected right hind limb was mostly compensated by the contra-lateral hind limb although a smaller portion was also compensated by the right front limb and the tail. The window of weight bearing deficit in MIA rats was well enough to assess effects of analgesics at any time point between Day 2 to Day 28. Effects were mainly assessed during the first or fourth week based on previous reports that pain in the early phase of the model mainly involves synovial inflammation while pain in later phase involves structural damages in the joint. Tramadol, morphine and dexamethasone were effective in both early and late phase of the model while naproxen and celecoxib were effective only during the early phase. Moreover, continuous administration of dexamethasone from Day 2 to Day 28 blocked joint pain development in the later phase of the model. Repeat dosing over 3-4 days was often required for optimal efficacy by the analgesics in this model. The relative ineffectiveness of the NSAIDs naproxen and celecoxib in the later phases supports the previous literature reports in this model and mimics clinical situation where effectiveness of NSAIDs gradually declines as OA progresses. The present results also suggest usefulness of the weak opioid tramadol as an analgesic in NSAID-refractory OA pain in clinic.

Disclosures: **H. Rashid:** None. **J. Douville:** None. **R. Samadfam:** None.

Poster

145. Pain Models: Pharmacology

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Program#/Poster#: 145.29/FF11

Topic: D.03. Somatosensation: Pain

Title: MEA recordings in rat spinal cord slices for applied pharmacological investigations

Authors: *E. STEIDL, F. GACKIERE, F. MADDALENA, B. BUISSON
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Abstract: NEUROSERVICE has developed a unique spinal cord slice preparation from young and adult rats. SC slices are prepared from 1 to 8 week old Sprague-Dawley rats and recorded with Multi-Electrode Arrays (MEA). Sustained spontaneous activities can be recorded at multiple electrodes placed either in dorsal or ventral horns. In ventral horns the spontaneous firing activity can be enhanced by micromolar concentrations of nicotine. In the dorsal horns, the spontaneous firing activity can be enhanced by Capsaicin in a dose-dependent manner with an apparent EC_{50} of 100 nM. The enhanced firing activity induced by 100 nM capsaicin is very stable over one hour of recording and this “steady-state” could be used to investigate the pharmacological activity of “pain-killer” molecules in a situation that could be compared as an artificial painful situation. We observe that 10 µM Morphine is able to shut-down the Capsaicin-induced firing activity over a couple of minutes application onto the slice. We have documented

the pharmacological properties of other well-known pain killers such as Oxycodone and the anti-epileptic drug Gabapentine. The spontaneous - as well as the Capsaicin-induced - firing activity is also modulated by Octreotide, a relatively specific agonist of Somatostatin type-2 (SSTR2) receptor. Our assay illustrates its wide potency for the *in vitro* investigation of the functional pharmacological activity of new pain-killer molecules.

Disclosures: **E. Steidl:** None. **F. Gackiere:** None. **F. Maddalena:** None. **B. Buisson:** None.

Poster

146. Motion: Physiology

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Title: Context-dependant directional suppression in visual motion processing

Authors: *T. MUKHERJEE, L. C. OSBORNE
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Abstract: Image motion is an important cue for parsing and reacting to visual scenes, and thus may depend on scene structure and behavioral goals. Here we ask how the brain weights motion across space and over time to estimate a global motion vector across a range of stimulus forms that differ in spatial statistics. We exploit the close connection between visual motion estimates and smooth pursuit eye movements to compute spatial temporal filters that predict the pursuit and perceptual discrimination of motion stimuli. While an ideal observer would simply add all motion signals equally to estimate a global motion vector, we find that the primate visual system modulates the contributions of different portions of the visual field in a stimulus-dependent manner. We created spatial and temporal variation in random dot kinetograms such that each dot shares a common motion direction and speed, with an added stochastic perturbation in motion direction updated synchronously every 40ms. The stochastic component of each dot's motion creates spatial and temporal variation in motion direction. We compute the correlation between motion fluctuations in the stimulus and eye in segments of the visual field.
Previous studies have shown that motion in the visual periphery (> 4 degrees from the fovea) can switch from enhancing to suppressing motion discrimination as luminance contrast increases. We

use the pursuit gain, the peak eye acceleration during pursuit initiation to quantify motion sensitivity. As the scale of certain stimuli grow, pursuit gain diminishes. We compute an index of suppression from the relative gains for stimuli with radii of 2.5 and 7 degrees. The surround suppression phenomenon has been attributed to antagonistic center-surround receptive field structure in motion-sensitive cortical neurons that dominate at higher contrasts. We find that the form of the spatial filter is not well described by a central region and a concentric surround. Rather, directional anisotropies arise soon after motion onset such that locations along the direction of motion - ahead of the eye during pursuit - are weighted positively whereas motion behind the eye is suppressive, even within 5 degrees of the fovea. The spatial filter is highly dependent on the form of the motion stimulus. High entropy (or high energy) stimuli like diffuse random dot patterns do not drive suppression whereas low entropy stimuli like gratings and checkerboards do cause suppression.

Disclosures: T. Mukherjee: None. **L.C. Osborne:** None.

Poster

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Title: Adaptive temporal coding of motion information in MT area and smooth pursuit

Authors: *B. LIU[1], L. C. OSBORNE[2]
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Abstract: In a noisy environment, the brain must integrate sensory signals over time to guide behavior. Differences in noise levels and temporal correlation time scales both in the stimulus and in neural responses determine the ideal time scale over which the system should integrate. Here we explore the temporal efficiency of a sensory code and movement behavior. We use as our test bed recordings of motion sensitive units in extrastriate cortical area MT of monkeys and

their smooth pursuit eye movements. In previous work we have shown that there is little variation in the eye movements that does not appear to arise from variation in visual motion estimates. Estimates of target motion derived from the MT population are tightly coupled to pursuit eye movements. Changes in motion variance – for example in the scale of direction fluctuations – drive rapid changes in response gain in MT neurons such that they maximize motion information. Rapid adaptation in cortex also optimizes pursuit behavior, maximizing information and minimizing tracking errors. Here we explore how motion correlation time, rather than variance, affects coding in MT neurons and in pursuit. We recorded extracellularly from isolated units in area MT of fixating monkeys with coherent random dot kinetograms with a time varying motion direction projected in the excitatory receptive field. Direction fluctuations were stochastic, updating on time scales from 10 to 120ms. We computed the linear transfer function between spike count and motion direction in a translating time window to characterize the temporal filter that best predicts the neural response over time. We find that the duration of the neural filters varies inversely with the update interval of the motion stimulus. Thus stimuli that are randomly updated on fast timescale are integrated over a longer time period than those that update less frequently. We performed pursuit experiments with the same monkeys tracking similar stimuli that translated across the screen with stochastic perturbations in trajectory. We find the same inverse relationship between behavioral filter duration and target motion correlation time that we observed in MT neurons, suggesting that motion estimates from the MT population reflect the integration profiles of individual units. The changes we observe in the neural filters are consistent with an adaptation process rather than nonlinearity in visual motion processing. Saturating non-linearities can mimic many features of adaptation, particularly in adaptation to variance, but saturation predicts the opposite trend in filter duration than we observe in MT and in pursuit – an increase in duration with increasing correlation time.

Disclosures: **B. Liu:** None. **L.C. Osborne:** None.

Poster

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Title: Analysis of variation in pursuit eye movements implies 2D motion vector decoding from MT population

Authors: *M. V. MACELLAIO[1], B. LIU[1], L. C. OSBORNE[2]
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Abstract: Sensory neurons typically encode information about multiple stimulus features: sound frequency and pressure level, color and orientation, etc. This multiplexing of stimulus features creates a multidimensional code that has an ambiguous mapping between firing rates and stimulus values. Past study of sensory decoding models has largely focused on single parameter estimation performance. We extend that analysis to a two-feature code, using a combination of cortical and behavioral recording and simulation to constrain models of how efficiently two independent stimulus features can be decoded from a sensory population. Our test bed is a population of motion-selective neurons in monkey extrastriate cortical area MT. MT neurons are tuned for the direction and speed of retinal image motion. The brain derives estimates of target direction and speed from the population of MT neurons to generate motion percepts and to drive visuomotor behaviors like smooth pursuit. Pursuit is an eye movement behavior triggered by retinal image motion that rotates the eyes to stabilize the image. In previous work we and others have shown that pursuit is tightly coupled to visual estimates of target direction and speed derived from MT population. Over 90% of the variation in pursuit is attributable to visual errors in estimating target motion direction, speed and onset time. We use dimensionality reduction analysis of eye trajectories in response to motion steps in different directions and speed to recover scalar direction and speed errors for each movement. We find that even when target directions and speeds are presented in random combinations, errors in eye direction and speed are correlated from movement to movement. Models of motor noise fail to reproduce the correlations we observe in behavior, suggesting they arise upstream, from the joint decoding of target direction and speed from the MT population. Joint decoding would also be more computationally efficient. MT populations encode more information about the joint direction-speed motion vector than the sum of information about direction and speed separately. We find that a 2D maximum likelihood decoder recovers more information about the motion vector (direction and speed) than do two 1D decoders recovering direction and speed independently. This feature-based synergy is preserved in pursuit: more information can be recovered about the target vector (direction and speed) than the sum of the information about target direction and speed individually.

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Poster

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Title: Motion perception in the common marmoset

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Abstract: Studies of motion perception have advanced our understanding of neural population coding and perceptual decision-making in the primate brain. The common marmoset offers new opportunities to probe these population codes at the circuit level because the relevant motion-processing areas (e.g., MT/MST) are all on the cortical surface, making them accessible to neural recordings with electrode arrays and imaging techniques. However, little is currently known about the perceptual abilities of the marmoset.
We trained two marmosets to perform a motion identification task: they reported the perceived direction of motion of a noisy random dot-pattern with a saccade to a “target ring”. Monkeys fixated a 0.6° diameter target at the center of the screen. After a random delay, a motion stimulus (black dots on gray background, 40 dots per frame, 0.2° diameter dots, dot lifetime 50 ms) was presented within a circular aperture (7° in diameter) centered on the fixation point and surrounded by a more peripheral target ring. The monkeys were rewarded for saccades to the target ring that were consistent with the target stimulus direction (reward was maximal for directional errors < 8° and decreased for larger errors, with no reward given for errors > 28°). To manipulate the difficulty of the task we varied the range of dot directions on each trial by sampling the direction of each dot from a Gaussian distribution. The mean of this distribution defined the target direction and was uniformly drawn from one of 50 equally spaced directions (spanning 0-360°). The variance of the Gaussian distribution defined the range of dot directions. Both monkeys learned to perform this task over 6 months of training and showed reductions in angular error throughout learning. Performance depended systematically on task difficulty and showed a typical trade-off between speed and accuracy, with slower reaction times for increased difficulty. Both monkeys exhibited decreased sensitivity in the oblique directions and had a directional bias that favored leftward and rightward directions for low coherence stimuli. Their performance was comparable to that of humans in terms of absolute error. This paradigm, in

combination with large-scale recordings, offers new opportunities to study the neural population code underlying motion perception and decision making.

Disclosures: S.L. Cloherty: None. **J.L. Yates:** None. **G.C. DeAngelis:** None. **J.F. Mitchell:** None.

Poster

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Title: Sub-threshold and spiking responses of marmoset area MT neurons to moving patterns

Authors: *J. PATTADKAL[1], B. SCHOLL[2], B. LI[3], N. J. PRIEBE[4]
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Abstract: Object movement often contains multiple features which must be integrated to be able to accurately infer motion direction and speed. An example of this process is the integration of motion signals in a drifting plaid, in which the direction of pattern motion may be inferred from the direction of the underlying grating components. Most motion selective neurons in the primate area V1 only respond to the motion of individual grating components but in area MT there are neurons that integrate motion signals and signal pattern motion. To investigate how neurons in marmoset area MT integrate motion signals, we performed in vivo whole cell recordings to access both the structure of the synaptic inputs as well as the spiking output. We recorded from MT pattern cells, which integrate the multiple motion signals, as well as component cells, which respond to single motion signals. For both pattern and component cells, the direction selectivity of the membrane potential was systematically less than that of spike rate, consistent with an increase in selectivity due to the spike threshold nonlinearity (mean Vm DSI = 0.35, SR DSI = 0.78, DSI=P-N/P+N). Component cells were more directionally-selective than pattern cells. One model for how MT pattern cells emerge is that motion in non-preferred directions is suppressed in pattern cells (Rust et al, 2006). We found that pattern cells depolarized at the orthogonal orientation and we did not observe responses below baseline indicative of inhibition. Instead we found trend for pattern cells to have broader selectivity than component cells, consistent with their integrative responses to complex motion signals. These records provide critical constraints

for how motion signals are integrated in area MT to construct a coherent sensation of object motion.

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Support: EY011488

Title: An imbalance of excitation and inhibition underlies direction selectivity in ferret visual cortex

Authors: *D. E. WILSON, B. SCHOLL, D. FITZPATRICK
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Abstract: Individual neurons in primary visual cortex respond selectively to the direction of motion of visual stimuli. Previous studies have shown that weak biases in co-tuned excitatory and inhibitory inputs are amplified by a spike threshold nonlinearity to generate robust direction selectivity in thalamorecipient layers of the visual cortex, but mechanisms of direction selectivity in other cortical layers have remained largely unexplored. In vivo two photon imaging of spine calcium signals in single direction-selective neurons in layer 2/3 of ferret visual cortex reveals that direction selective neurons receive excitatory synaptic inputs tuned to both the preferred and null directions, albeit with a bias for the preferred direction. Despite an abundance of null-tuned excitatory synaptic inputs, in vivo whole-cell patch clamp recordings show that the subthreshold responses of layer 2/3 neurons with strong spiking direction selectivity exhibit only modest depolarization to the null direction of motion. Indeed, conductance measurements demonstrate that excitation and inhibition operate in an imbalanced regime such that excitation and inhibition do not scale with each other during stimulation at the preferred and null directions, contrary to what has been shown in cells residing in thalamorecipient layers. Such highly selective membrane potential tuning may arise from null-direction tuned inhibition from direction-tuned inhibitory neurons in distant cortical columns. To explore this possibility, we labeled axons of inhibitory neurons with GCaMP6s and imaged their visual responses. We found direction-selective boutons projecting to domains of the direction preference map tuned to the opposite direction of motion. We then used patterned optogenetic stimulation to activate inhibitory neurons in direction domains and measure functional connectivity with excitatory neurons using whole-cell patch clamp recording. These mapping experiments reveal robust inhibitory

connectivity spanning multiple cortical columns, including columns that prefer the direction of motion opposite to that of the recorded cell.

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Poster

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NEDO

Title: Temporal resolution of early visual processing in macaque monkeys estimated from short-latency ocular following responses

Authors: *A. TAKEMURA[1], K. MIURA[2]
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Abstract: The sense of motion is analyzed by the visual system. Recently, it was reported that two-frame apparent motion stimuli induced short-latency ocular following responses (OFRs) in humans. It was suggested that energy-based motion analyses represented by a motion energy model (Adelson and Bergen, 1985) that involves temporal filters with biphasic impulse response functions underlie OFRs. To further understand the neural substrates underlying visual processing to elicit OFRs, it is critical to have an appropriate animal model. In this study, we conducted two experiments on two macaque monkeys (*Macaca fuscata*) to infer temporal resolutions of the visual system by quantitatively identifying the kernels of the filters based on OFRs.
OFRs were elicited in the two monkeys by the two-frame apparent motion stimuli of a vertical sinusoidal grating (spatial frequency, 0.25 cycles/°; Mickelson contrast, 32%). Eye movements were recorded by electromagnetic induction. Each trial was initiated by presenting a small fixation spot on a uniform gray background. After the left eye was positioned within ±1.5° of the fixation target for a brief randomized period, a grating appeared as a background of the fixation spot. In the first experiment, a 90° step of the grating was presented with various inter-stimulus intervals (ISIs; 0–640 ms). In the second experiment, a 90° step of the grating was applied with various durations of the initial image frame [motion onset delays (MODs), 10–640 ms].

In the computational analyses, we calculated changes in the eye position during the 50-ms interval starting from 50 ms after the onset of motion as response measures; the parameters shaping the kernels of the temporal filters and the amplitude of the output were optimized using the motion energy model.
We found that OFRs of monkeys were qualitatively consistent with previous findings regarding the dependence of OFRs on ISIs/MODs in humans. The first experiment showed the presence of inverted OFRs to 90° steps of gratings presented with ISIs, as was observed with motion percepts. The second experiment suggested that longer exposure to the stationary image prior to visual motion reduces the driving signals of OFRs, as was observed with the post-saccadic enhancement of OFRs. The motion energy model reproduced the characteristics of OFRs under different ISIs/MODs after quantitatively optimizing the parameters of the temporal filters of the model. Furthermore, the kernels of the best-fit temporal filters were biphasic with optimal frequencies of 10.9–13.7 Hz, suggesting that temporal resolutions of the visual system in monkeys were slightly higher than those in humans (6.7–8.0 Hz).

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Poster

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Title: Encoding of pattern motion in macaque area MT

Authors: *C. QUAIA, I. KANG, L. M. OPTICAN, B. G. CUMMING
LSR, Natl. Eye Inst., Bethesda, MD

Abstract: When presented with moving textured patterns, direction-selective neurons in early visual cortex are sensitive to the direction of motion of individual oriented signals in the pattern, not of the pattern itself (the aperture problem). In area MT some cells behave similarly (component cells), but others respond to the direction of motion of the whole pattern (pattern cells), solving the aperture problem. The distinction is quantified using a Pattern Index that compares the responses to a single drifting grating with those to plaids composed of two drifting gratings. However, based on this measure, many cells are unclassed (equally compatible or incompatible with both computations). Recently, unikinetic plaids (UPs), obtained summing a drifting and a static grating having different orientations, have also been used to quantify pattern selectivity in MT. However, the pattern index based on this stimulus also yields a large number of unclassed cells. We leveraged UPs in a novel way that allowed us to identify cells that

perform a partial computation of pattern disparity. We compared responses to two unikinetic patterns each composed of a drifting and a static 1-D noise pattern. The static pattern was rotated either +45deg or -45deg relative to the moving pattern. A component cell would respond equally to the two plaids, whereas tuning curves to the two stimuli rotated by 90deg would signal a pattern cell. Intermediate rotations signal a partial computation of pattern motion. We recorded from 138 MT neurons in two macaque monkeys. 21 showed qualitatively different responses to the two UPs, so could not be easily characterized with our rotation measure. Of the remaining 117, 11 behaved like component cells (rotation not significantly different form 0) and 14 behaved like pattern cells (rotation not different from 90 deg). Most cells (92) exhibited a partial rotation, between 0 and 90deg but significantly different from both. In 101 cells with both measures, we found a positive correlation ($r=0.52$, $p<1e-7$) between the angle of rotation measured with UPs and the pattern index computed from responses to bikinetic plaids. However, of the 56 cells classified as component cells with bikinetic plaids, 47 showed rotations significantly greater than zero. Of 36 cells described as unclassed by the pattern index, 2 showed no rotation with UPs, 30 showed an intermediate rotation, and 4 showed a complete rotation (not significantly different from 90). This highlights a limitation of the pattern index - it only compares two models, which might both provide poor fits. This suggests that the computation of pattern motion occurs in a graded way across MT neurons.

Disclosures: **C. Quaia:** None. **I. Kang:** None. **L.M. Optican:** None. **B.G. Cumming:** None.

Poster

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Title: Development of simple and complex motion processing in ferret higher order visual area PSS

Authors: *A. A. LEMPEL, K. J. NIELSEN
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Abstract: Due to its immature state at the time of birth and the complexity of its visual system, the ferret is an ideal model for studying the development of visual processing. In the past, developmental studies have been limited to early stages of the visual system, including the primary visual cortex (V1). Recently, we have characterized complex motion properties in PSS, a higher order visual area in the ferret brain, opening the possibility of studying the functional development of more advanced stages of the visual system. PSS neurons display simple motion

properties (such as direction selectivity) along with complex motion responses. In particular, responses to transparent random dot stimuli and coherent plaids reveal signatures of motion opponency and motion integration in PSS. In this study, we investigate the developmental timelines of simple and complex motion properties in PSS, and their relationship to other aspects of ferret visual system development. Data were collected in anesthetized ferrets using single cell recording techniques or two-photon calcium imaging. Our results indicate that PSS direction selectivity reaches full maturity after just 4 days of visual experience at postnatal day (P) 36. Critically, the previously observed higher degree of direction selectivity in PSS than V1 is already apparent during the first 2 days after eye opening. These findings suggest that PSS circuitry is capable of enhancing the direction selectivity of its principal input as soon as visual experience begins. In terms of complex motion responses, PSS motion opponency seems to be present and fully developed right after eye opening. In contrast, the analysis of responses to plaid stimuli demonstrated that pattern responses are absent in PSS for 4 more days after mature direction selectivity is reached (around P40). After this time point, pattern responses develop quickly and reach mature levels within the following 2 days. As a step towards investigating the mechanisms shaping this developmental time course, we have begun to study the effect of controlled visual stimulation on the development of both simple and complex motion properties in PSS. Exposing ferrets to drifting gratings right before eye opening (P28-30) for several hours resulted in a significant increase in direction selectivity. Similarly, exposing ferrets to plaids right before natural emergence of pattern responses (P38-41) led to an increase in pattern responses. Future experiments will build on this controlled stimulus paradigm to identify critical components of the motion pathway development.

Disclosures: A.A. Lempel: None. **K.J. Nielsen:** None.

Poster

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Title: Predictive activity in the ventral intra-parietal area of macaque monkeys

Authors: *J. CHURAN, A. KAMINIARZ, F. BREMMER
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Abstract: The ventral intraparietal area (VIP) of the macaque is one of the major stages in processing of self-motion information. Neurons in this area have been shown to code for the direction as well as speed of visually simulated self-motion. We tested, how the activity of VIP-

neurons changes if the onset of the visually simulated self-motion is self-initiated or passively induced. For this we trained a macaque monkey to press a button when the color of a fixation point changed. The button press initiated a stimulus that simulated a self-motion through a 3D cloud of random dots. The heading of the motion was either in the preferred direction of the recorded neuron or in directions 30 degrees clock- or counter-clockwise. The button press either started the simulated self-motion immediately (Motion-onset asynchrony, MOA=0 ms, 'active condition') or the start was delayed by a random duration (MOA = 500 - 1000 ms, 'passive condition'). So far we collected 65 VIP-neurons from one monkey from which 49 provided sufficient data for the analysis. We found that although the visual responses to the self-motion were not significantly different for self-initiated and passively experienced self-motion, there was a significant ($p<0.05$) anticipatory activity that started on average 500 ms after the button press. This anticipatory activity was statistically confirmed ($p<0.05$) for a sub-population of 16/49 (33%) of the recorded neurons. We conclude that area VIP is not only responsible for bottom-up processing of complex visual stimuli but may also provide the neuronal basis for cognitive functions like imagery and/or prediction of self-motion. This prediction of passively experienced self-motion is of a high ecological relevance since it allows the organism to prepare for processing of sensory signals associated with a sudden onset of motion.

Disclosures: **J. Churan:** None. **A. Kaminiarz:** None. **F. Bremmer:** None.

Poster

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Title: Mapping complex receptive field visual motion preferences in primate cortical area MSTd

Authors: A. MAAMOUN[1], B. WILD[1], *S. TREUE[2,3,4]
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Abstract: Area MSTd in primate extrastriate visual cortex is assumed to play a central role in the encoding of optic flow stimuli, i.e. the large-scale motion patterns on the retina caused by the movement of the visual environment relative to an organism. Correspondingly, MSTd neurons show bell-shaped tuning to linear motion, as well as to 'spiral motion' (a continuous circular

space of complex motion patterns including expansion, contraction and rotation). In addition, some MSTd cells have been reported to be position-invariant in their responses to spiral motion stimuli, indicating a high degree of non-linearity in their receptive field structure.
Here we report a study aimed to determine the exact motion patterns MSTd neurons are most responsive to. We used large complex random dot motion patterns and reverse correlation, a linear method which has been successfully used to characterize receptive fields in earlier cortical areas V1 and MT. We investigated whether these patterns allow a fuller and more detailed description of the specific motion preferences of individual MSTd neurons, compared to the simple assumption of linear and/or spiral direction tuning. We also determined the position dependency of the MSTd responses to spiral motion patterns.
We recorded from more than 100 single MSTd cells in three rhesus monkeys, trained to foveate a fixation point on a backprojection screen. The reverse correlation stimuli were large complex random dot patterns, formed by the smooth variation of local dot direction and speed between a grid of positions in the stimulus where the local parameters were chosen randomly every 100ms from all possible directions and a large range of speeds.
For ~20% of the cells the reverse correlation analysis recovered significantly structured spatial motion preference profiles. We are investigating whether limiting the reverse correlation stimulus to the most active parts of the receptive field yields reverse correlation maps for a larger proportion of cells.

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Poster

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Title: Stable functional networks during natural vision in the macaque brain

Authors: *M. ORTIZ-RIOS, M. HAAG, F. BALEZEAU, M. C. SCHMID
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Abstract: Functional connectivity assessment of BOLD signal co-fluctuations can provide valuable information about the brain’s large-scale network organization. In macaque monkeys such measurements are typically taken during rest or anesthesia. Therefore, to what extent brain networks adapt their functional connectivity during active processing of continuous sensory input remains largely unexplored. Here, we aim to identify functional networks involved in the processing of natural movie scenes during dynamic exploratory vision. To this end three awake-

behaving macaque monkeys (*Macaca Mulatta*) were accustomed to participate in functional magnetic resonance imaging (fMRI) experiments in a dedicated primate 4.7 Tesla vertical-bore magnet. Whole-brain gradient-echo EPI sequence (1.2 mm^3 isotropic voxels) data were acquired using a 4-channel phase array coil system. All EPI data were pre-processed for slice timing, motion correction and signal drift while anatomical data provided the basis to segment gray and white matter voxels. A digital template (Reveley, et al. 2016) of the Saleem and Logothetis atlas was used to further extract regions of interest and to ease the visual inspection and quantification of connectivity matrices. During fMRI scans monkeys were awake and actively viewed sequences of 30 s long movie clips interspersed with 30 s long periods of a black screen. The movies contained scenes featuring egocentric and exocentric motion with navigation in open spaces. Throughout the experiment monkeys were allowed to freely explore the visual scenes and execute eye movements, which were monitored with an MRI-compatible infrared camera. Initial analyses included general linear modeling of the BOLD response and coherence assessment between the BOLD signal and the visual stimulation paradigm. This revealed robust BOLD modulation (greater than 3% signal change) across visual and visually-related brain areas. Regions with significant visual activation included subcortical structures (SC, LGN, Pulvinar), primary visual (V1), higher visual cortical areas (V2, V3, V4, V6), motion sensitive cortex (MT/FST), ventral stream regions (TEO, TE, TPO) and visuo-motor related areas in parietal and premotor cortices (LIP and FEF). In a second step we measured functional connectivity using Eigenvector centrality during different movie periods and identified functional hubs in MT/FST, TE/TPO, LIP and FEF that were replicable and stable across experimental repetitions and individual monkeys. Overall our preliminary results suggest that functional networks typically assessed during rest are stable and robust during natural vision.

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Topic: D.07. Vision

Title: Effects of active movements on perception of moving plaids: Integration versus segmentation

Authors: *G. SEDDA, S. P. SABATINI, V. SANGUINETI
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Abstract: The interplay between action and perception has suggested that the motor and perceptual systems may ‘educate’ each other. The underlying mechanisms are not yet fully understood. In fact, there are many evidences that information required by the motor system to

produce movements also affects the way object motion is visually perceived. This effect is likely more significant, the greater the uncertainty of perceptual information. The interpretation of plaid stimuli moving through an aperture is inherently ambiguous, because they can be perceived as single patterns moving coherently, or as two superimposed gratings, which slide over each other in different directions. It has been suggested that the perceptual decision between integration and segmentation is not a feedforward process. Rather, it relies on the competitions between the neural representations of these opposite interpretations of the stimulus. Differently, actions do not suffer from this ambiguity because they are integrative by nature. We reasoned that the perceptual uncertainty caused by moving plaids may be influenced by the active interaction between the observer and the stimulus, so actions may bias the perceptive decision towards either integration or segmentation. The experimental apparatus consists of a robotic manipolandum and a screen: the subject is seated at about 50 cm in front of the screen and performs planar movements while grasping the handle of the robot. At the same time the subject is exposed to the visual stimuli displayed on the screen. Perceptual uncertainty may be modulated by varying the stimulus parameters that are the transparency and the directions of the gratings relative to each other, and the overall direction of the plaid movement. To test the effect of exercise on perception of plaid movements, we designed a motor task in which the observer had to interact actively with the plaid, by directly generating the relative movement between the plaid and the aperture. A perceptual judgment test was performed before and after the active interaction phase to verify and quantify its effect. Results show that action affects perception in a wide range of conditions, and this effect can be characterized by this procedure.

Disclosures: G. Sedda: None. **S.P. Sabatini:** None. **V. Sanguineti:** None.

Poster

146. Motion: Physiology

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 146.14/GG3

Topic: D.07. Vision

Support: NIH Grant R01EY022443

Title: Responses of neurons in cortical area MT to multiple stimuli moving at different depths are biased toward the stimulus component at the near disparity

Authors: J. XIAO, *X. HUANG
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Abstract: Segmenting visual scenes into distinct objects and surfaces is fundamental to vision. Both visual motion and depth cues are important for image segmentation. We investigate how multiple stimuli moving in different directions at different binocular disparities are encoded by

neurons in monkey extrastriate area MT. The visual stimuli were two overlapping random-dot patches moving in two directions separated by 60° or 120°. One stimulus component was presented at a near disparity (-0.1°) and the other at a far disparity (0.1°). To measure the tuning curves of neurons in response to the bi-directional stimuli, we varied the vector averaged direction of the two stimulus components across 360°. Trials of 60° and 120° angular separations between the two stimulus components were randomly interleaved. Also interleaved were the individual stimulus components that constituted the bi-directional stimuli. The animal performed a direction discrimination task and was required to report the motion direction of the stimulus component at a cued disparity by making a saccadic eye movement to one of twelve targets in the direction matching the stimulus direction. We recorded from 59 MT neurons from one macaque monkey while the animal performed this task. We found that the behavioral performance for discriminating the direction of the near component of the bi-directional stimuli was slightly but significantly better than that for the far component. The neuronal response tuning to the bi-directional stimuli can be well accounted for by a weighted sum of the responses elicited by the individual stimulus components plus a multiplicative interaction term between the two component responses. Consistent with the behavioral bias, we found that the tuning curves of MT neurons in response to the bi-directional stimuli showed a strong bias toward the near component. The response weight for the near component was significantly greater than that for the far component. At 60° angular separation, the population-averaged response weights for the near and far components were 0.71 and 0.43, respectively ($p < 10^{-11}$). At 120° separation, the weights for the near and far components were 0.84 and 0.49, respectively ($p < 10^{-14}$). We found the same bias toward the near component regardless whether the neurons preferred a near or far disparity. The response bias toward the near component persisted even when the animal attended to the far component of the bi-directional stimuli, suggesting that the bias was not due to attention. Our results reveal a dominant effect of near stimulus component on the neural representation of multiple visual stimuli and provide new constraints on neural models of image segmentation.

Disclosures: **J. Xiao:** None. **X. Huang:** None.

Poster

146. Motion: Physiology

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Topic: D.07. Vision

Support: NIH R01 EY022443

NIH R01 DC013698

Title: Why tuning curves of neurons in cortical area MT for multiple motion directions have both symmetric and asymmetric shapes

Authors: W. HUANG[1], X. HUANG[2], *K. ZHANG[3]
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Abstract: Neurons in the middle temporal (MT) area of the primates are highly selective to the direction of visual motion. The directional tuning curve of an MT neuron for a single movement direction typically has a symmetric Gaussian shape. We are interested in MT responses to stimuli with multiple motion directions because this study may eventually shed light on how visual system extracts motion information to segment moving objects. For two sets of overlapping random dot stimuli moving in two separate directions, primate observers are able to segregate the two direction components and perceive motion transparency. In our neurophysiological recordings, we have found that the responses of MT neurons in macaque monkeys to two overlapping direction components separated by an angle of 45º or more have four general types: The first type has a symmetric tuning curve that is approximately the average of the responses to single motion components. The next two types have asymmetric tuning curves with peak positions biased either clockwise or counterclockwise from the midline. The fourth type has a double-peaked tuning curve that is typically also asymmetric. Due to the symmetry of the stimulus setup, one would naively expect that the responses should also be symmetric. We seek to investigate theoretically whether the asymmetric shapes of the tuning curves may have any computational advantages in the processing of visual motion with multiple components. We have developed an efficient maximization method for Shannon mutual information between random moving stimuli and the elicited responses of a population of MT neurons with independent Poisson spikes. The optimal shapes of the tuning curves were obtained by optimizing the parameters of an underlying feedforward network model, and the key parameters here are the connection weights between a lower layer of V1-like units with directional responses and a layer of MT units. In the optimization procedure, no information about the experimental tuning curves was ever used to constrain the model and the theoretical MT tuning curves could potentially take any form. After an unsupervised learning process, all four types of tuning curves that resembled the experimental data emerged spontaneously. This result suggests that the population coding in area MT might be optimized for dealing with visual motions with multiple components. This optimal solution requires a mixture of diverse types of neurons with both symmetric and asymmetric tuning curve shapes. Our information-theoretic method used here is quite general and could potentially be extended to related problems of optimal neural population coding.

Disclosures: **W. Huang:** None. **X. Huang:** None. **K. Zhang:** None.

Poster

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Topic: D.07. Vision

Support: DFG CRC/TRR-135/A2

Title: Dynamics of heading-encoding in macaque areas MST and VIP

Authors: *F. BREMMER[1], M. LAPPE[2], J. CHURAN[1]
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Abstract: The control of self-motion through an environment is of utmost importance in everyday life. Previous studies have clearly demonstrated that the medial-superior-temporal area (MST) and the ventral intraparietal area (VIP) of the macaque monkey are critically involved in the encoding of self-motion information. Furthermore, we and others have shown before that the response properties of neurons in areas MST and VIP are well suited to decode heading direction from neural activity. Computations in these studies, however, were typically based on activity from long response intervals. Here we were interested to determine the dynamics of heading encoding, i.e. to answer the question how fast neurons can encode heading direction and if this time-course would in principal be suited for navigation.
Experiments had previously been performed in three trained macaque monkeys. Self-motion stimuli were back projected onto a tangent screen and covered the central 90° of the visual field. Across trials, optic flow sequences (2500ms) simulated self-motion over an extended horizontal plane at 1m/s in one of three directions: 30° to the left, straight-ahead, and 30° to the right. Monkeys had to fixate throughout the trials. The three different self-motion directions were combined with three different gains (G) of simulated eye movements: G = 0.0 (fixed gaze), G = 0.5 (aiming at the natural viewing behavior, and G = 1.0 (imitating perfect tracking of a ground-fixed target). Stimulus-induced steady-state population activity of neurons from areas MST and VIP was used to train a linear decoder model. We applied this model to the time courses of the population activity for the nine different experimental conditions.
Confirming previous results, population activity allowed to decode simulated heading in the fixed gaze condition (G = 0.0). Importantly, also in the simulated eye-movement conditions (G = 0.5 or 1.0), heading could be decoded reliably. The time-course of the decoded heading for self-motion directions -30° and 30° allowed to fit exponential functions. Time-constants of these functions were typically smaller than 200ms.
We conclude that heading encoding in macaque areas MST and VIP is fast and well suited to encode heading in everyday living. Importantly, functional equivalents of both areas have been

identified in humans. This provides further evidence for a critical role of primate areas MST and VIP for navigation.

Disclosures: F. Bremmer: None. **M. Lappe:** None. **J. Churan:** None.

Poster

147. Visual System: Responses During Behavior

Location: Halls A-C

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Program#/Poster#: 147.01/GG6

Topic: D.07. Vision

Title: Visually-cued eyeblink conditioning reveals cortical circuits underlying sensorimotor transformation

Authors: *L. TANG, G. LUR, J. A. CARDIN, M. J. HIGLEY
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Abstract: The encoding of external sensory stimuli by neocortical circuits is central to the coordination of perception and behavior. However, the cellular mechanisms underlying sensorimotor transformations are poorly understood. To elaborate circuits underlying sensorimotor signaling, we developed a visually-cued eye blink conditioning (VEBC) paradigm that requires conditioned stimulus (CS) representation in primary visual cortex (V1). We trained mice to associate a small sinusoidal drifting grating with a brief unconditioned stimulus (US) comprising a corneal air puff. Awake head-fixed mice readily exhibit predictive blinking after a short training period, and experiments utilizing either lesions or acute muscimol infusion demonstrate that V1 is necessary for both learning and performance of the behavior. The task is highly sensitive to stimulus properties, as varying visual contrast results in modulation of performance. Additionally, trial-to-trial variability in arousal, measured as either pupil diameter or locomotion, is correlated with task performance, enhancing behavior when stimulus contrast is close to the perceptual threshold. To further investigate the neuronal activity in V1 during behavior, we carried out longitudinal 2-photon calcium imaging of V1 cells, revealing that subpopulations of neurons exhibit diverse patterns of activity reflecting both task learning and performance. Different neurons encode either the CS or US with both increases or decreases in activity. Interestingly, the majority of layer 2/3 neurons steadily reduce their evoked responses during learning, suggesting increasing sparseness of sensory representation. In contrast, layer 5 neurons increase their activity with learning. Using retrograde fluorescent labeling and viral tracing, we demonstrated that layer 5 cells can be divided into largely non-overlapping groups based on projecting to either the pons, the superior colliculus, or the dorsal striatum. Given the established role of the pons and cerebellum in eyeblink conditioning, we hypothesize that corticopontine neurons may play a central role in this form of sensorimotor behavior. We are currently testing the necessity and sufficiency of these specific circuits using a combination of

retrograde viral expression and optogenetic manipulation in behaving animals. In summary, VEBC serves as a simple and useful task for dissecting the neocortical circuitry underlying sensorimotor coordination.

Disclosures: L. Tang: None. **G. Lur:** None. **J.A. Cardin:** None. **M.J. Higley:** None.

Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Support: The Israeli Science Foundation

The Israeli Ministry of Science

Title: Novel System for studying natural and artificial vision in behaving rats

Authors: *T. ARENS-ARAD, N. FARAH, Y. MANDEL
Ophthalmic Sci. and Engin. Lab. Manager The Mina & Everard Goodman Facul, Bar Ilan Univ., Ramat Gan, Israel

Abstract: Purpose
Recording visual cortex responses to natural or prosthetic visual stimuli in behaving rodent is important for basic and translational research. Here we present the development of a head-mounted projection system integrated with electrodes for recording visual evoked potentials (VEP) in response to natural and artificial stimulus in awake and behaving animals.
Methods
We devised and customized a Digital Mirror Device (DMD) based head-mounted system, to project high quality images at visible and near IR light right onto the rat retina, by a periscope-like optical system. Computer simulations were performed by Zemax software in order to characterize and optimize the optical properties of the system. The design fitted onto the rat skull using a customized head plate and adaptor. VEPs were recorded using electrodes implanted over the primary visual cortex and embedded into the mounting head plate. VEPs induced by flashes with varying pulse durations (ranging from 0.25msec to 8msec), varying frequency (ranging from 1Hz to 32Hz) and by stimulus with varying luminance contrast levels, projected by the head mounted projector while the animals were both anesthetized and awake.
Results
The system enabled the projection of good quality images (MTF values higher than 0.85 at pupil diameter of 1mm), with a retinal image diameter of 3mm corresponding to 45 degrees visual field in the rat. Robust VEP signals were recorded in response to images projected at various

contrast and light intensity. The VEP amplitude decreased as a function of temporal frequency reaching the noise limit for frequencies higher than 32Hz and increased as a function of stimuli duration, reaching a plateau at pulses longer than 10ms. Similarly, a decrease in VEP amplitude for decreasing contrast was also observed, reaching the noise level at 6% contrast. For stimulus with varying luminance contrast levels the VEP amplitude increased both for "on" and "off" responses reaching a plateau at a contrast level of 65%**.**

Conclusions

The feasibility of investigating natural and artificial visual function performance in awake and behaving rats was demonstrated using this novel head-mounted projection system. This method could be used for the evaluation of various treatments or other interventions, such as training for the studying of visual cortex plasticity in awake and behaving animals both in natural and artificial vision.

Disclosures: T. Arens-Arad: None. **N. Farah:** None. **Y. Mandel:** None.

Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Support: NWO VIDI Grant 864.10.010

Title: Behvaioural response of mice to over-head sweeping stimuli

Authors: *A. TAFRESHIHA, S. VAN DER BURG, J. A. HEIMEL
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Abstract: Background: When a raptor is flying at a high altitude, the only sensory modality available to a mouse to detect it, is vision. It has been shown that mice respond to such stimuli by freezing or fleeing depending on the features of the stimuli and the availability of a shelter. In this study, we aimed to quantify the behavioural response of mice to sweeping over-head stimuli that mimic a bird of prey in a freely moving condition. Furthermore we were interested in how animals change their behaviour by habituation upon repeated exposure to the stimuli.
Methods: Male, adult Bl6 mice were placed in a Plexiglas box wherein they could roam freely. A LCD screen was placed over the top of the box to present the stimuli. The stimuli consisted of a black disc or hawk, 5 degrees of visual angle that swept the length of the screen at the average speed of 30 deg/s for 3 seconds. The response of the mice were recorded via a camera placed underneath the behaviour arena and later analyzed with a custom-made program in Matlab.
Results: All mice tested respond to the sweeping stimuli by freezing, which was defined as a

period of at least half a second that the mouse movement decreased to 30% of average over 10 seconds before the stimulus onset. We observed that mice show more and longer duration freezing to the stimuli at the start of the session compared to the end, indicating that they became habituated to the stimuli. Furthermore, mice showed clear habituation to the stimuli over days, reaching a plateau in last few sessions. We then looked at the persistence of the habituation by not showing the stimuli to the mice for several weeks. The habituation was extinguished and mice started freezing again when stimuli were presented. However the habituation was recovered quickly by being exposed to the stimuli a few times.
Conclusions: We found that mouse defensive responses habituate after repeated exposure to stimuli resembling a flying bird. This observation shows that mice can still learn to adjust their costly innate defensive responses by means of simple learning through adaptation, as mice likely perceive the stimuli to be biologically irrelevant. This learning mechanism seems to be dynamic since mice show extinction of their habituation after a period of non-exposure. It has previously been shown that looming stimuli induce a freezing response by means of a neuronal circuitry involving the superior colliculus, thalamus, amygdala and PAG. We speculate that a similar circuit is engaged and habituated for sweeping stimuli.

Disclosures: A. Tafreshiha: None. **S. van der Burg:** None. **J.A. Heimel:** None.

Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Support: NIMH INC fellowship

Title: Selective optogenetic activation of inhibitory interneurons in area V1 of the Rhesus Macaque causes rapidly reversible perceptual suppression

Authors: *M. AVERY[1], S. BEN-HAIM[2], J. DIMIDSCHSTEIN[3], G. FISHELL[3], J. H. REYNOLDS[4]
[1]Salk Inst., San Diego, CA; [2]Neurosurg., UCSD, San Diego, CA; [3]Dept. of Neurobio., Harvard Med. Sch., Boston, MA; [4]SNL-R, The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: Inhibitory interneurons play critical roles throughout the brain and their dysfunction has been implicated in brain disorders such as schizophrenia and autism. In the mouse a variety of tools, have been developed to enable cell-type-specific patterns of protein expression, including fluorescent markers, calcium indicators and opsins. This has made it possible observe and modulate the activity of various classes of neurons, and to elucidate some of their roles in neural computation. It has been more challenging to achieve cell-type specific targeting of

neurons in the non-human primate. A number of studies have distinguished putative pyramidal neurons from fast spiking interneurons based on action potential shape, revealing their differential roles in processes such as attention (Mitchell et al, 2007). The CAMKII promoter has been used, in concert with viral tropism, to cause selective expression in pyramidal neurons (Han et al, 2009), and this has been used to test specific hypotheses about neural computation in the primate brain (Nassi et al, 2014). However, there has not been a reliable way to achieve selective expression in primate interneurons. We recently (Dimidschstein et al, 2016) introduced a new enhancer-based strategy to express proteins in interneurons. Here, we have used this strategy to activate interneurons in the primary visual cortex of the alert macaque. We find that optogenetically activated neurons tend to be narrow spiking, consistent with activation of PV+ interneurons, which make up ~75% of all GABAergic neurons in primate V1. Some broad spiking neurons, putative broad-spiking interneurons, also exhibit short-latency optogenetic responses. We also find a number of neurons whose responses to visual stimuli are strongly suppressed, due to activation of inhibition. Further, optogenetic activation of inhibitory neurons in V1 leads to a spatially selective perceptual deficit, as reflected in a strong and consistent increase in contrast detection thresholds. This work demonstrates a novel way to identify inhibitory neurons in primates through optogenetic tagging and to reversibly inactivate a region of the primate brain with high spatial and temporal resolution.

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Poster

147. Visual System: Responses During Behavior

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Yale, Brown-Coxe Fellowship

Title: Distinct optimal waking states for sensory responses in primary visual cortex and visual detection performance

Authors: *G. T. NESKE[1], D. A. MCCORMICK[1,2]
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Abstract: Sensory-evoked responses in neocortex strongly depend on the spontaneous, ongoing state of cortical neuronal networks. In waking animals, cortical state is closely related to

behavioral variables such as arousal and sustained attention. Recent work in awake, head-fixed mice has begun to shed light on state-dependent cortical sensory processing. Our group previously described the cortical synaptic correlates of the optimal waking state for sensory processing in the mouse primary auditory cortex (A1) (McGinley et al., *Neuron*, 87: 179, 2015). Specifically, using pupillometry to monitor a wide spectrum of waking states, we found that the highest signal-to-noise ratio, gain, and reliability of sound-evoked spiking and membrane potential (Vm) responses in A1 neurons occurred at a state of intermediate arousal without locomotion. This optimal state was associated with hyperpolarized Vm and low Vm variance. Congruously, mice also exhibited optimal performance on an auditory detection task at this state. An open question is, to what extent does the state-dependence of optimal sensory responsiveness and sensory signal detection uncovered in the auditory system pertain to other sensory modalities? Here, we describe the state-dependent properties of spontaneous and evoked spiking and Vm responses in cortical neurons in mouse primary visual cortex (V1), as well as state-dependent performance on a visual detection task. We find that, similar to A1 neurons, spontaneous spiking activity in V1 neurons is lowest and Vm most hyperpolarized during intermediate arousal without locomotion. Unlike in A1, however, Vm variance in V1 neurons decreased with arousal and was lowest during locomotion. Visually evoked responses of V1 neurons to Gaussian white noise movies generally exhibited an increase in gain and reliability with arousal, with the highest values occurring during locomotion. Interestingly, behavioral performance on a target-in-noise visual detection task (similar in structure to our previous auditory detection task) was optimal during intermediate arousal without locomotion, similar to the previous results for auditory detection performance, but seemingly contrasting with our data for the state-dependence of visually evoked responses in V1. The apparent mismatch between the optimal state for evoked responses in V1 and the optimal state for visual detection behavior indicates that the neuronal basis for the latter might not be inherent to primary sensory cortical responses but perhaps to state-dependent dynamics in downstream cortical areas that integrate both sensory- and decision-related information.

Disclosures: **G.T. Neske:** None. **D.A. McCormick:** None.

Poster

147. Visual System: Responses During Behavior

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Human Frontier Science Program to JF

Marie Curie to JF

Wellcome Trust / Royal Society fellowship to ABS (200501)

Title: Simultaneous representations in visual cortex and hippocampus

Authors: *J. FOURNIER, A. B. SALEEM, M. J. WELLS, K. D. HARRIS, M. CARANDINI
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Abstract: Animals rely on multiple navigational signals to estimate their position in an environment. They can use vision to update their estimate based on visual landmarks. They can also perform path integration, i.e. estimate the distance they traveled by integrating speed signals from vision and self-motion. Path integration and visual landmarks both contribute to the spatial representation in hippocampus (e.g. Gothard et al 1996). However, it is yet unclear whether navigational signals influence neural processing in sensory areas like the primary visual cortex (V1).

We trained mice to lick in a specific position of a virtual reality corridor for water reward, while head-restrained on a running wheel. On 30% of trials, the gain of the virtual environment was changed so the animal had to run 20% more, or less, to reach the reward location, while visual landmarks remained at the same position along the corridor. Mice learned this task in 6-8 weeks and used both visual cues and path integration: they licked in position intermediate between those dictated by visual cues and by path integration.

While the mice performed the task, we recorded simultaneously from V1 and CA1 neurons, yielding recordings from >50 well-isolated neurons in each area. To assess the relative contribution of visual cues and path integration to neural responses, we used a Bayesian decoder to predict the animal's position from either V1 or CA1 population activity.

Comparison across gain conditions showed that the position encoded by CA1 place cells was intermediate between being driven by visual cues or path integration alone, consistent with the animal's behavior. The balance between path integration and visual cues was not constant across space: it tended to be more biased toward vision as the animal approached the reward location.

Surprisingly, V1 response profiles tiled the entire corridor and often had a clear preference for a single location , yielding a decoding accuracy comparable to CA1 although visual landmarks were repeated in different positions along the corridor. Moreover, decoding from V1 neurons in the different gain conditions revealed a bias similar to that observed in CA1: the average trajectory decoded from the V1 population was intermediate between predictions based on visual cues and path integration.

Our results thus suggest a control of V1 activity by path integration. We propose that this control could rely on feedback position signals from the navigational system (e.g. hippocampus or medial entorhinal cortex) or on a direct influence of the distance travelled by integrating visual flow and self-motion signals.

Disclosures: J. Fournier: None. **A.B. Saleem:** None. **M.J. Wells:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

147. Visual System: Responses During Behavior

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Wellcome Trust / Royal Society 200501

EPSRC EP/F500351/1

Title: Mapping navigation-related signals in mouse visual areas

Authors: *E. M. DIAMANTI, K. D. HARRIS, A. B. SALEEM, M. CARANDINI
Univ. Col. London, London, United Kingdom

Abstract: Vision provides signals to guide navigation, and navigation in turn influences visual input. Accordingly, cortex devotes neurons to the joint processing of signals related to vision and navigation. Such processing is seen in parietal cortex, but may begin as early as in primary visual cortex (V1), where neurons integrate visual flow with locomotion signals. Do navigation signals become progressively stronger in areas joining V1 to parietal cortex? Are these areas part of a stream that transforms visual information into navigation-related signals?
We used 2-photon calcium imaging to record activity of 33,811 neurons across 4 visual (V1, LM, AL, PM) and 3 parietal areas (RL, A, AM), while head-restrained mice ran along a corridor in virtual reality.The corridor contained two landmarks (grating or plaid) repeated after 40 cm, creating two visually identical sections. Imaging sessions involved two conditions: (1) closed-loop, where the speed of the virtual corridor (virtual speed) matched the animal's run speed; (2) open-loop, where previous closed-loop visual scenes were played back to the animal regardless of its running speed.
In closed-loop, most cells responded to specific landmarks. Neurons in V1 and LM responded similarly to visually identical landmarks, typically showing two peaks separated by 40 cm. Such repeated activity was less prominent in parietal areas (RL and A), with a population in parietal cortex preferring to fire at a single virtual position.
The combination of position and speed explained responses better than position or speed alone. The effect of position and speed could be captured by a multiplicative model. The relative influence of position or speed varied among areas. V1 and LM responses were modulated mostly by position (and the associated visual pattern), while responses in parietal areas were modulated mostly by speed.

To understand the degree to which speed-modulation in each area depended on physical locomotion vs. optic flow, we turned to the open-loop condition. Neurons in V1 and LM exhibited positive weights for both speeds, with a bias towards virtual speed. Instead, some neurons in parietal cortex exhibited negative weight for one of the two speeds, with a bias towards run speed. Therefore, neurons in V1 and LM code predominantly for visual flow, whereas many neurons in parietal cortex code for signals related to self-motion.
Our results suggest a hierarchical organization for processing of navigation-related signals in visual areas, where activity in areas lower in hierarchy, V1 and LM, is predominantly modulated by visual variables, while higher regions reflect a translation of this information to navigational signals.

Disclosures: E.M. Diamanti: None. **K.D. Harris:** None. **A.B. Saleem:** None. **M. Carandini:** None.

Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Title: A Brain Observatory for visual behavior: Development and scaling of a change detection task in mice

Authors: *M. GARRETT, P. A. GROBLEWSKI, J. T. KIGGINS, D. R. OLLERENSHAW, S. MANAVI, S. CROSS, D. WILLIAMS, S. MIHALAS, S. R. OLSEN
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Detection of moment-to-moment changes in the visual scene is fundamental to an animal's ability to navigate the world. We have developed a go/no-go change detection task in which images are presented serially and mice must respond to changes in the visual stimulus to earn rewards. We show that head-fixed mice can be trained on this task within a few weeks and that they can detect changes in a diverse set of visual stimuli (e.g. oriented gratings and natural scenes), permitting a range of experimental questions. We aim to systematically measure activity in the visual cortex during performance of this task using a standardized 2-photon imaging pipeline (Allen Brain Observatory: http://observatory.brain-map.org/visualcoding/). The change detection task affords a variety of stimulus conditions and behavioral states that can be related to simultaneously recorded neural activity. To ask how coding of visual information depends on behavioral states, including arousal, task engagement, and expectation, data streams including eye tracking, locomotor activity, movies of body position and licking behavior will be collected during task performance. Stimulus identity and behavioral choice on single trials can be compared to neuronal responses to investigate how sensory information is transformed from

perception to action. As the change detection task requires a comparison between current and prior stimuli, it enables exploration of the temporal dynamics of visual representations. By imaging the activity of populations of single neurons across multiple visual cortical regions, cell classes, and cortical depths, this study will provide a comprehensive survey of information processing in visual cortical circuits during visual behavior in mice. As part of the Allen Institute's commitment to open science, the data generated through this project will be made publicly available for download and use by the neuroscience community to drive progress in understanding the neural basis of perception and behavior.

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Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Title: The incorporation and uses of eye tracking in a large-scale pipeline for the allen institute's brain observatory

Authors: *E. K. LEE[1], M. RAMADAN[2], J. D. LARKIN[2], C. WHITE[2], F. GRIFFIN[2], K. ROLL[2], T. NGUYEN[2], S. CALDEJON[2], S. CROSS[2], W. B. WAKEMAN[2], N. SJOQUIST[2], J. PERKINS[2], D. FENG[2], S. E. DEVRIES[2], C. SLAUGHTERBECK[2], D. SULLIVAN[2], D. WILLIAMS[2], D. MILLMAN[2], N. H. CAIN[2], G. K. OCKER[2], P. LEDOCHOWITSCH[2], A. STEGER[2], R. VALENZA[2], K. MACE[2], S. WHITESIDE[2], E. LIANG[2], L. NG[2], C. FARRELL[2], M. A. BUICE[2], J. LECOQ[2]
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Abstract: Understanding the brain requires more than a census of its genes or a catalog of its parts - one needs to observe it in action as it performs the tasks that give rise to perception and behavior. In 2016, the Allen Institute for Brain Science launched the Allen Brain Observatory: it is the first tool of its kind to provide a highly standardized survey of cellular activity in the mouse visual system. Interrogating all these functional cell types, layers, and areas of the mouse visual cortex necessitates the performance of hundreds of experiments in a uniform manner with careful orchestration and standardized operational processes. In these experiments, eye position plays a key role in quantifying visually evoked neuronal responses. To precisely map the visual receptor fields of individual neurons using *in vivo* two photon calcium imaging, one must be able to disentangle the effects of eye position on said visual responses.To address these concerns, we present an integrated experimental platform, eye tracking algorithm, data quality control, and

operational procedure for use in infrared video-oculography and gaze analysis as part of a scalable workflow. This system allows us to reliably collect eye tracking data and is compatible with multiple recording modalities (two photon calcium imaging, wide-field imaging, and electrophysiological recordings) in a high-throughput context (>10 mice/day). We demonstrate its ability to record pupil and gaze position across a large number of mice, different rigs, and different experimental operators. This integrated platform has allowed us to precisely map the eye gaze location across many hundreds of passive viewing sessions and to correct for the effects of gaze position on receptor field mapping.

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Poster

147. Visual System: Responses During Behavior

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Charles H. Revson Biomedical Research Fellowship

Title: Behavioral and neurophysiological characterization of visual crowding in macaques

Authors: *C. A. HENRY, A. KOHN
Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Visual crowding is a phenomenon whereby the features of objects viewed peripherally are rendered less discriminable by adjacent objects in the visual field. Crowding has been well studied in humans; yet little is known about crowding in animal models where neurophysiological recordings are experimentally tractable.
We have previously shown (Henry and Kohn, Cosyne 2015) that stimulus displays that cause crowding can reduce orientation information in neuronal populations in primary visual cortex (V1) of anesthetized macaques. In order to relate underlying physiological changes to measures of behavioral crowding, we trained three animals to perform a demanding fine orientation

discrimination task, under control and crowded conditions. The target stimulus was a small (1.1-1.3 deg diameter) drifting sinusoidal grating presented for 250ms. Animals judged the orientation of the target (relative to a learned 45 deg reference) and indicated their percept via a saccadic eye movement to one of two choice targets that appeared a few hundred milliseconds after stimulus offset. On a subset of trials, the target stimuli were crowded by distractor gratings of similar size, placed adjacent to the target. The orientations of the distractor stimuli were offset a few degrees from the 45 degree reference (some tilted vertical, some horizontal). Behavioral crowding effects were similar in nature and magnitude to those seen in human observers.
We recorded from small groups of neurons in V1 of one animal while he performed the perceptual discrimination task. On average, neuronal responses were weakly suppressed when targets were presented with distractors, but many neurons showed response facilitation. Individual neuronal variability was relatively unchanged under crowding; as such, there was little change in discriminability at the single neuron level. We used trial-by-trial co-fluctuations between the neurons' responses and the animal's decisions (i.e. choice probability) to test for a change in behavioral readout of V1 signals. A small fraction of neurons showed significant choice probabilities; however there was no marked relationship between neuronal selectivity and choice probability, nor changes in choice probability under conditions of crowding.
Our results suggest that the modulation of V1 neuronal responses by distractors plays a role in crowding, but that changes in the encoding or decoding of downstream cortical populations are likely to be the major contributors.

Disclosures: C.A. Henry: None. **A. Kohn:** None.

Poster

147. Visual System: Responses During Behavior

Location: Halls A-C

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Topic: D.07. Vision

Support: JHU Science of Learning

Title: Visual psychophysics in the ferret

Authors: E. L. DUNN-WEISS, *K. J. NIELSEN
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Abstract: The ferret is one of the primary animal models for cortical development research, in particular the development of visual cortex. Indeed, ferrets are born with their eyes closed, and do not open their eyes until around postnatal day 32. Thus, the development of ferret visual cortex before and after eye-opening is accessible to experimental investigation and manipulation. Yet, despite the significance of the ferret model for visual development and a growing body of

literature dedicated to the functional characterization of neurons in ferret visual cortex, relatively little is known about the adult ferret's behavioral visual capabilities. Here, we report the behavioral performance of adult ferrets on a battery of visual psychophysical tasks that evaluate visual acuity, motion and form perception. Ferret visual acuity was assessed by determining contrast sensitivities for detection and orientation discrimination tasks at different spatial frequencies. Additionally, we measured just-noticeable-differences for fine orientation discriminations about vertical and oblique reference orientations. Ferret motion perception was evaluated both with random-dot kinematograms (RDK) with different coherence levels, and with gratings drifting at different speeds. These paradigms allowed us to determine thresholds for motion coherence and for speed, respectively. Finally, form perception was evaluated based on discriminations between horizontal and vertical glass patterns at different coherence levels. All behavioral tasks were designed as freely-moving two-alternative forced-choice (2AFC) tasks, though a headfixed equivalent is currently being developed. Ferrets performed above 80% on the easiest condition on all tasks on average. In addition, their performance systematically varied with task difficulty in all tasks, so that psychometric curves could be fit with high fidelity. Thus, ferrets demonstrate the capability to reliably perform a variety of visual tasks that range in complexity. This broadens the possibilities for visual development research, as future experiments may test the effect of manipulations during development on any of these visual capabilities. Furthermore, this extensive characterization of the visual behavioral capabilities of the adult ferret may facilitate comparison with other animal models that are prominent in visual neuroscience, such as primates, cats, and mice.

Disclosures: E.L. Dunn-Weiss: None. **K.J. Nielsen:** None.

Poster

147. Visual System: Responses During Behavior

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Support: NEI DP1EY024503, R01EY011787

SIMPLEX N66001-15-C-4032

ARO W91NF-12-1-0594 (MURI)

Title: Modulation of behavioral performance by targeted activation of cortical ensembles in mouse primary visual cortex

Authors: *L. CARRILLO-REID[1], S. HAN[1], W. YANG[2], R. YUSTE[2]
[1]Biol. Sci., [2]Columbia Univ., New York, NY

Abstract: Cortical ensembles in primary visual cortex are coactive groups of neurons that respond to visual stimuli and are also active spontaneously. Ensembles can be artificially imprinted through optogenetics and recalled by single cell stimulation, demonstrating pattern completion. The functional connectivity of these ensembles could generate an internal representation of the surrounding world. Thus, learned visual behavioral tasks could originate by recalling of neuronal ensembles from primary visual cortex. However, it remains unknown whether it is possible to manipulate visually guided learned behaviors by the targeted activation of cortical ensembles. In order to study the modulation of behavioral performance induced by the selective activation of cortical ensembles with single cell resolution we used simultaneous two-photon optogenetics and two-photon imaging of neuronal populations in awake head-fixed mice performing a Go/No-Go task. We used probabilistic graphical models to identify and target high-ranked neurons with pattern completion capability in cortical ensembles. Selective photoactivation of ensemble neurons associated with the Go signal positively modulated behavioral performance whereas photoactivation of randomly selected neurons negatively modulated it. Our findings demonstrate the possibility of manipulating functional neuronal ensembles to influence behavioral choices.

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Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Title: Neuronal computations underlying orientation change detection in the mouse visual cortex

Authors: *M. JIN, L. GLICKFELD
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Abstract: The ability to detect a change in the environment is critical for survival. Understanding the perceptual constraints on change detection will not only help us to determine what strategies the brain adopts to accomplish this task, but may also reveal the relevant circuits and their organization. Here we aim to investigate the computation performed when detecting a change of visual stimulus orientation. Two models based on the visual information encoded in the mouse primary visual cortex (V1) were tested: one is an orientation identification model which takes a scaled and summed response across an orientation tuned population to decode whether the baseline or target orientation was most likely presented; the other model supposes a temporal comparison in which each neuron's distribution of responses to the baseline and target orientations are discriminated. As adaptation is an intrinsic component of change detection, we use it as a tool to first predict the impact of adaptation on the animal's ability to detect

orientation changes under these two models and then determine which model is consistent with the actual effects of adaptation on behavior. Using two-photon calcium imaging, we found that adaptation reduces the neuronal responses, and repels the preferred orientation away from the adapting orientation. Thus, under the orientation identification model, adaptation makes the perceived orientation tilted away from the adapting baseline orientation resulting in an improvement of orientation change detection. However, the temporal comparison model suggests a lower discriminability between responses to baseline and target orientations due to adaptation of responses to stimuli close to the adapting stimulus, and therefore predicts an impairment of change detection with adaptation. Our behavioral data shows that adaptation increases the animal's orientation change detection threshold and is consistent with the temporal comparison model. However, we find that the behavior is only dependent on the interval immediately preceding the stimulus, suggesting that the comparison being made is with an internal template rather than the response to preceding stimuli. Overall, this study reveals that adaptation impairs performance on a change detection task and proposes a possible computation underlying visual change detection. Indeed, the temporal comparison proposed here can be computed using a generalized circuit organization and therefore might be adopted across sensory modalities to detect changes of variety sensory stimuli.

Disclosures: **M. Jin:** None. **L. Glickfeld:** None.

Poster

147. Visual System: Responses During Behavior

Location: Halls A-C

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Topic: D.07. Vision

Title: The implications immersive virtual reality usage on the visual system

Authors: *R. ESQUENAZI[1], R. MOSHER[2], J. BUENROSTRO[3], S. LUNDQVIST[4], S. A. DREW[4]
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Abstract: Asthenopia, or visual discomfort, is a condition related to performing near work tasks such as reading or viewing a computer screen. Symptoms can include headaches, sensitivity to light, or eye strain (Borsting et al., 2003). There are two oculomotor systems that are critical to near work performance; the accommodative system and the vergence system. Insufficiencies in these two systems have been found to contribute to visual discomfort symptoms (Sheedy et al., 2003). Two surveys have been used to assess insufficiencies in these systems: (a) the Visual Discomfort Survey (VDS) developed by Conlon et al. (1999) and (b) the Convergence

Insufficiency Symptom Survey (CISS) developed by Borsting et al. (2003). Advancements in technology have seen an accompanying report of visual discomfort symptoms reported with computer use and virtual reality (VR) displays (Ames et al., 2005). The emergence of immersive VR systems has been met with increased popularity. One such system is the Oculus Rift, affording the user the opportunity to integrate physical movement into virtual space while mirroring real life movement. Given the increasing availability of these systems, it is important to understand how immersive VR usage affects the visual system. In this study participants with experience using immersive VR were recruited, and a battery of questionnaires was administered consisting of the VDS, CISS, and a Virtual Reality Symptom Survey (Ames et al., 2005). Results found that as VDS scores increased, a participant was more likely to report having engaged in a longer VR session (1 hr. or more). Additionally, as VR body and eye symptoms increased, a participant had a higher likelihood of having increased VDS scores. These findings have widespread implications in the field of neuroscience research, given that the Oculus Rift is being utilized in several different domains that include assessment of chronic neuropsychological and movement disorders, balance assessment in Parkinson's disease, and evaluation of outcomes for adults following a stroke (Lewis & Rosie, 2012; Morel et al., 2015; Galvin et al., 2011). Due to these findings, it is important to assess the possible connection between negative impacts on the visual system and sustained VR usage before VR technology becomes readily available to a wider market of consumers.

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Poster

147. Visual System: Responses During Behavior

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Topic: D.07. Vision

Title: Examining accommodative changes after using head mounted virtual immersion displays

Authors: *R. MOSHER[1], J. MIER[3], N. URENDA[3], A. ILNICKI[2], B. HACKNEY[3], D. A. DEL CID[4], S. A. DREW[3]
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Abstract: Numerous virtual reality platforms have recently been introduced to the market offering an immersive experience, but there is little research investigating how this technology may affect users' visual systems. With a growing number of applications ranging from commercial gaming to potential therapeutic rehabilitation of movement disorders, there may be interest in knowing if any possible risks might be associated with continued use (Yelshyna, et al.,

2016; Just, Stirling, Ros, Naghdy, & Stapley, 2016). Head-mounted stereoscopic displays on current virtual reality systems introduce novel demands on ocular motor systems due to a mismatch between accommodation and vergence depth cues, which may result in visual discomfort (Carnegie & Rhee, 2015). Participants reported significantly increased visual discomfort after 30 minutes using Oculus Rift in immersive virtual reality compared to pre measures before use. Additionally, some participants showed markedly different patterns in accommodative response, the process in which the lens of the eye changes in thickness to maintain focus on a target. As immersive virtual reality had direct implications across neuroscience, including potential for pain control in burn patients (Hunter, et al., 2014), phantom limb pain management (Dunn, Yeo, Moghaddampour, Chau, & Humbert, 2017), and post stroke sensorimotor rehabilitation (Badia, Fluet, Llorens, & Deutsch, 2016), these findings suggest further investigation in ocular motor function related to immersive virtual reality use may be warranted.

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Poster

147. Visual System: Responses During Behavior

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Topic: I.04. Physiological Methods

Support: Ball Venture Grant

UE Innovation/Reinvestment Grant

Title: Human physiological arousal comparison: Pupillometry and galvanic skin response

Authors: S. C. DUFRESNE, N. A. BROOKHOUSE, A. M. MURPHY, N. R. NICHOLS, *L. A. BECKER
Psychology, Univ. of Evansville, Evansville, IN

Abstract: Physiological arousal can be measured using both pupillometry (pupil diameter) and galvanic skin response (electrodermal activity). However, discrepancies between the two techniques may lead to misleading study comparisons. The two techniques were explored to determine which is the more accurate measure of arousal for future research. 47 participants were configured to Gazepoint eye-tracking software, as well as connected to NEULOG GSR logger sensor electrodes on their fingers. Participants were shown a 60-second video consisting of a series of 15 images at 2-second intervals, with a 2 second blank screen in between each photo. The images were selected from the IAPS database, where emotional and physiological

response ratings were already measured and quantified, insuring a baseline for reliability. 12 images were excitatory and 3 were included for baseline measurements. Participant data was then compiled for both pupillometry and GSR for each photo to compare fluctuations in response between the two. The GSR and pupillometry data showed a negative trend over time, indicating that overall arousal decreased the longer the participants were exposed to the stimuli; however, the pupillometry showed more apparent activations and responses. This indicates that pupillometry is a more sensitive measure of arousal than GSR. Additionally, data is presented as a regression equation that allows conversion of GSR data into pupillometry data and vice versa.

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Poster

148. Visual Cortex: Circuits and Populations

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Title: Measuring cell-type specific layer 4 connectivity using high throughput conjugate array tomography and targeted multi-patch electrophysiology

Authors: *F. C. COLLMAN[1], B. R. LEE[1], A. D. BADEN[2], S. DAVIS[1], O. GLIKO[1], T. KARLSSON[1], M. M. NAUGLE[1], K. PARKER[1], E. PERLMAN[3], J. SCHARDT[1], R. SERAFIN[1], S. SESHAMANI[1], G. J. SOLER-LLAVINA[4], R. BURNS[2], S. J. SMITH[1]
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Computer Sci., Johns Hopkins Univ., Baltimore, MD; [3]Johns Hopkins, Baltimore, MD; [4]Novartis Inst. For Biomed. Res., Cambridge, MA

Abstract: Understanding the detailed relationship between the structure of anatomical connectivity and its functional physiological response at the level of individual connections between individual neurons is difficult to obtain directly. Multi-whole cell electrophysiology can obtain detailed information about the functional strength, frequency and dynamics of individual connections between neurons. However, obtaining the corresponding single synapse anatomical measurements has proven difficult because the complex and extended architecture of the brain's synaptic networks demands high resolution imaging of large volumes. We have been developing approaches to address this problem through technologies designed to improve the throughput of array tomography, including robotic assisted section collection, microfluidic staining, high speed wide-field immunofluorescence imaging, targeted conjugate imaging by field-emission scanning

electron microscopy, and automated volume assembly. We'll provide an overview of these technological improvements and how we are applying them to exploring connectivity in layer 4 of the mouse visual cortex. We'll also present data that compares and contrasts functional and anatomical characterizations of connectivity between two distinct genetically defined cell types in layer 4 (Scnna1a-Tg3 and RorB).

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Poster

148. Visual Cortex: Circuits and Populations

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Support: Gracious support of Paul G. Allen

Title: Investigation of synaptic connectivity in mouse visual cortex by two-photon optogenetic stimulation

Authors: *C. A. BAKER, A. BOSMA-MOODY, T. A. HAGE, G. J. MURPHY
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The Allen Institute for Brain Science is pursuing an in-depth characterization of connectivity between neurons in mouse visual cortex via several experimental approaches. One such method characterizes up to 56 potential synaptic connections through the simultaneous recording of 8 neurons in an acute slice preparation. While this strategy provides ground truth for determining synaptic weight between neuronal pairs, it is inherently low throughput and only samples a very small subset of the potential connections in a slice. As a complementary approach, we are developing a platform for high-density sampling of putative connections across a wide range of interneuronal distances via two-photon optogenetic techniques. Using rapid spiral scanning of a 1060nm diffraction-limited spot over the soma of neurons expressing the highly sensitive, red-shifted opsin ReaChR, we achieve spike probabilities of 95% at powers of 30mW at the sample. The spatial specificity of two-photon activation leads to a dramatic reduction in spike probability when the photoactivation spiral is targeted off the soma, demonstrating a lateral resolution of 12 microns. The measured axial resolution of roughly 30 microns, however, may lead to off-target effects when ReaChR expression is dense. We routinely achieve spike latencies of 20ms with millisecond jitter, and are exploring holography and temporal focusing light sculpting techniques to further improve temporal resolution.

Combining patch clamp recording of up to four neurons with optogenetic stimulation of hundreds of putative presynaptic cells, we have observed multiple examples of both inhibitory and excitatory connections and can measure the degree of common input to a network of connected cells across different genetically defined neuronal cell types. We are examining the resulting data with template matching, deconvolution, and inference algorithms to robustly detect synaptic events when the exact timing of the presynaptic action potential is unknown and/or the signal is corrupted by direct photoactivation of the recorded cell. The ongoing optimization and application of these methods show promise in contributing to the systematic characterization of connectivity in mouse visual cortex.

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Poster

148. Visual Cortex: Circuits and Populations

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Title: Connectivity in L5 of mouse primary visual cortex using a multi-patch pipeline

Authors: P. A. DAVOUDIAN, A. HOGGARTH, L. CAMPAGNOLA, *S. SEEMAN, M. SCHROEDTER, C. FARRELL, H. ZENG, R. LARSEN, G. J. MURPHY, T. JARSKY
Allen Inst. for Brain Sci., Seattle, WA

Abstract: A cortical wiring diagram is required to understand the contribution of individual cell types to neural circuits that drive behavior. However, even in well-studied brain regions such as primary visual cortex (V1), large-scale, cell-type specific connectivity information is lacking. To address this need, we developed a high-throughput multi-patch pipeline as part of the *In Vitro* Synaptic Physiology Characterization (IVSPC) program at the Allen Institute for Brain Science. During initial pipeline development we constructed three semi-automated, production multi-patch rigs which integrated many pieces of custom hardware and software. We tested this complex system by probing a 5x5 connectivity matrix among specific excitatory and inhibitory cell types including Tlx3, Sim1, Sst, Pvalb, and Vip in layer 5 of adult mouse V1 slices. We performed up to eight simultaneous whole-cell patch clamp recordings while providing stimulation trains at various frequencies, and in just four months probed over 2,000 potential connections with 7% connection rate. Additionally, this dataset will allow us to describe connection strength and dynamics under various experimental conditions. Achieving consistent performance using this approach required the expertise of electrophysiologists, engineers,

transgenic colony managers, and trained tissue processors. Key components for success included design of 1) custom hardware and 2) software, 3) breeding of specific transgenic mouse lines, and 4) establishing standard protocols. The IVSPC production rigs were custom built to identical specifications thereby reducing experimental variability. Two pieces of custom software increased experiment speed and reliability. The ACQ4 multi-patch module automates pipette movement and tracking while the MIES package for Igor Pro enables simultaneous recording from many channels, automated pressure regulation, and online analysis. Combined, these features increased the efficiency of obtaining multiple whole-cell recordings and the ability to detect connections. We took advantage of existing Allen Institute transgenic mouse lines and novel quadruple transgenic lines to target connections within and between specific cell groups. Standardization of data acquisition and analysis will give rise to a robust and reproducible high volume dataset with which we can detect weak and low probability connections that are often overlooked. In full production, the IVSPC pipeline will build upon this foundation to characterize a multi-layer connectivity matrix across cell types in mouse V1 as well as human brain samples to gain an in-depth understanding of local cortical circuits.

Disclosures: **P.A. Davoudian:** None. **A. Hoggarth:** None. **L. Campagnola:** None. **S. Seeman:** None. **M. Schroedter:** None. **C. Farrell:** None. **H. Zeng:** None. **R. Larsen:** None. **G.J. Murphy:** None. **T. Jarsky:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Support: NIH Grant U01MH105982

Title: Synaptic dynamics of the cortical layer 5 microcircuit

Authors: S. C. SEEMAN[1], L. CAMPAGNOLA[1], A. HOGGARTH[1], *P. A. DAVOUDIAN[2], G. J. MURPHY[1], T. JARSKY[1]
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Abstract: The dynamic properties of synapses determine the behavior of cortical circuits but are difficult to measure. Prior work using multi-patch recordings to characterize synapses have provided key insight into the function and organization of the cortical microcircuit. However, the low yield of these experiments has left us with an incomplete understanding of synaptic properties. Furthermore, results are often difficult to compare across studies due to differences in experimental conditions, analytic methods, and reporting. As part of the *In Vitro* Synaptic Physiology Characterization (IVSPC) program at the Allen Institute for Brain Science we

established a pipeline for multi-patch recording to characterize the strength, kinetics, and short-term plasticity of synapses. Although these experiments will address broad questions of cortical circuit structure, our initial emphasis was on generating data suitable for developing biophysical synapse models. Cells in mouse primary visual cortex were characterized by their morphology, cortical layer, and the presence of fluorescent reporters driven by one or two CRE-dependent promoters (Tlx3, Sim1, Pvalb, Sst, or Vip). We recorded postsynaptic currents evoked by action potential trains with temporal patterns chosen to explore induction and recovery of short-term plasticity for each synapse type. From these responses, we measured the average synaptic strength, kinetics, and short-term plasticity and related these to pre- and postsynaptic cell classes. Synaptic response amplitudes were fit to a set of pre-synaptic release models in order to characterize their short-term dynamics and to ensure the suitability of the data for use in network models. To facilitate comparison with prior results from the literature, we have also explored the effects of age, temperature, and external calcium concentration on synaptic properties. Our results provide the beginning of a comprehensive and detailed survey of cortical synaptic properties and their relationship to pre- and postsynaptic cell type.

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Poster

148. Visual Cortex: Circuits and Populations

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Title: Distinct functional roles of layer 2/3 Somatostatin-expressing inhibitory interneurons in mouse primary visual cortex

Authors: *L. LI, U. KNOBLICH, C. REID, H. ZENG, C. KOCH
Allen Inst. For Brain Sci., Seattle, WA

Abstract: Neocortical inhibitory interneurons expressing Somatostatin (SST) have been shown critical to sensory information integration, plasticity and learning, neural development and involved in several brain disorders. Although *in vitro* studies have demonstrated great diversity of SST neurons' morphology, physiology and transcriptomics, underlying mechanisms for SST neurons to contribute to cortical (micro)circuit construction and function remains largely unknown *in vivo*. We employed *in vivo* two-photon (2-p) targeted whole-cell recording and 2-p calcium imaging to characterize the intracellular membrane potential (Vm) dynamics in the primary visual cortex (V1) of transgenic mice in which SST neurons are fluorescently labeled.

We studied the spontaneous and visually evoked Vm and spiking activities of V1 SST neurons under light anesthesia, and how their activities were integrated within local networks. Our 2-p targeted whole-cell data showed in our recordings ~60% of V1 SST neurons had bi-modally distributed Vm dynamics (fluctuating between ~-70 mV and ~-40 mV), which was correlated with local network activity. These neurons were better-driven by visual stimuli. About ~40% L2/3 SST cells, however, had a uni-modal distribution of Vm (around ~-40 mV), were spontaneously active but showed low responsiveness to visual stimulation. More importantly, their Vm was uncorrelated to local network activity. Our data provided novel insights on how a major type of neocortical inhibitory interneuron is inter-connected and assembled into microcircuits for neural information processing.

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148. Visual Cortex: Circuits and Populations

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Program#/Poster#: 148.06/GG27

Topic: D.07. Vision

Title: Cortical processing of binocular information in the mouse

Authors: *H. H.-Y. HUANG, G. J. STUART
John Curtin Sch. of Med. Res., Canberra, Australia

Abstract: Visual information arising from the two eyes is integrated in the primary visual cortex (V1). Given that the vast majority of retinal projections (>95%) cross the mid-line, we surmised that cortical input from the ipsilateral eye is mediated primarily via an indirect callosal projection from contralateral V1. Using urethane anaesthetised adult C57BL6/J mice, we performed whole-cell recordings from pyramidal cells in the binocular region of V1 while illuminating either or both eyes using custom-made light-emitting diode (LED) “goggles”. As expected, neuronal responses were biased towards the contralateral eye (mean ocular dominance index = 0.46±0.06; n=60 cells). Importantly, we found that excitatory postsynaptic potentials evoked by illuminating the ipsilateral eye were delayed relative to those evoked by illuminating the contralateral eye (20% onset time: contralateral eye: 46.7±0.9 ms vs. ipsilateral eye: 65.4±2.2 ms; $p<0.0001$; n=40 cells), consistent with the notion that the visual input from the ipsilateral eye arises via a different and longer synaptic pathway than the contralateral input. In a different set of experiments, tetrodotoxin (TTX) was injected into V1 on one side while recording the local field potentials from V1 in both hemispheres. TTX injections abolished responses from either eye in the injected hemisphere and significantly reduced the ipsilateral eye response in the opposite hemisphere (39±14% reduction, n=3 mice). Taken together, our results suggest that the

ipsilateral visual input to binocular V1 contains a significant callosal projection from the contralateral V1. Experiments are currently underway to quantify the contribution of this callosal component to binocular processing of visual information using optogenetics in conjunction with whole-cell recordings.

Disclosures: H.H. Huang: None. **G.J. Stuart:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.07/GG28

Topic: D.07. Vision

Support: Chateaubriand Fellowship of the Office for Science & Technology of the Embassy of France in the United States

NIH Grant EY020765

European Community (Human Brain Project H2020-720270)

Title: Using network simulations to model intracellular membrane dynamics in V1 layer 4

Authors: *M. M. TAYLOR[1], D. CONTRERAS[2], A. DESTEXHE[3]
[1]Neurosci., Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA; [2]Neurosciience, Univ. Pennsylvania Sch. of Med., Philadelphia, PA; [3]CNRS, Gif-sur-Yvette, France

Abstract: Conductance measurements from intracellular recordings in vivo provide an estimate of synaptic activity in the network, and in particular how excitation and inhibition relate to each other. We have previously reported the dynamics of excitation and inhibition in simple cells of cat primary visual cortex (Area 17 or V1) in response to excitatory flashed stimuli, using intracellular recordings in vivo. Here, we use conductance-based network models of excitatory and inhibitory cells with in vivo-like behavior, in order to understand the role of baseline and visually driven network activity on the responses of single cells. The network model consists of regular-spiking (RS) and fast spiking (FS) cells, displaying asynchronous irregular spiking statistics similar to awake states (Vogels & Abbott 2005, Destexhe 2009, Zerlaut & Destexhe 2017). We adapt the network model to respond to realistic, visually-driven inputs from populations of LGN cells recorded in vivo in response to the same excitatory flashed stimuli from which the single-cell conductances were estimated.
We characterize the temporal dynamics and the correlations between excitatory and inhibitory conductances (gE and gI, respectively) in the simulations and compare them with the data. Our goal is to estimate and explore the amplification of LGN excitatory inputs by recurrent local cortical activity, which cannot be directly measured in vivo. We parametrically explore the

impact of network connectivity (random vs. topological) as well as the level of background excitatory input. High levels of background input generate a high-conductance state (depolarized Vm and asynchronous irregular firing), while low levels generate a low-conductance state (hyperpolarized Vm and mostly silent network).
We show that the high-conductance state of the network changes the spiking responses and the gain of the input-output transfer function of individual cells. We also find that delays between stimulus-evoked excitatory and inhibitory inputs are much longer in low than in high conductance states. Finally, topological compared to random connectivity also increases the gE-gI delay. We conclude that the network conductance state is a key determinant of sensory-evoked conductance dynamics and network spiking behavior.

Disclosures: M.M. Taylor: None. **D. Contreras:** None. **A. Destexhe:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.08/GG29

Topic: D.07. Vision

Title: Synaptic connectivity between neurons in the lateral geniculate nucleus and primary visual cortex by viral tools

Authors: *H. CHAN[1], D. C. W. CHAN[2], X. F. YANG[2], Y. KE[2], W. H. YUNG[2]
[2]Sch. of Biomed. Sci., [1]Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Activities from randomly sampled neurons in chosen pre- and post- synaptic CNS regions are often used in scientific studies to evaluate complex cross-region pathways such as thalamo-cortical pathways. These sampled activities are from neurons that may not necessarily have actual connections with each other. Combining current generation of viral techniques, the use of vesicular stomatitis virus (VSV) and the single cell electroporation procedure, selectively-targeted single-cell retrograde monosynaptic labelling can be achieved and provide more accurate and representative results. We applied these tools to re-evaluate certain aspects of the visual thalamo-cortical pathway. Custom-designed stimuli were presented to mice *in vivo*. Real-time fluorescence signals from calcium indicator GCaMP6f were captured under a two photon microscope setup to identify simple cells in the primary visual cortex (V1). Subsequent electroporation of retrograde glycoprotein RABV-G and TVA receptor encoding transgenes into the chosen cell(s) allow specific VSV infection. Existing studies that used locally injected viral or fluorescent labelling discovered that the V1 receives monocular input from the dorsal lateral geniculate nucleus (dorsal LGN). Revealing upstream neurons to an identified V1 simple cell provides detailed information with more specificity about its presynaptic LGN population

density and location, and enables further functional studies on the LGN-to-V1 thalamocortical network.

Disclosures: **H. Chan:** None. **D.C.W. Chan:** None. **X.F. Yang:** None. **Y. Ke:** None. **W.H. Yung:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.09/GG30

Topic: D.07. Vision

Support: NIH EY011488

NIH EY026273

Title: Circuit mechanisms for correlated spontaneous activity in visual cortex

Authors: ***G. B. SMITH**, D. E. WHITNEY, D. FITZPATRICK
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Abstract: In the visual cortex, long-range distributed networks span millimeters and show orderly functional organization when engaged with visual stimuli. Recently, we demonstrated that correlations in ongoing spontaneous activity exhibit a pronounced long-range structure, which can reveal both the local and global organization of these visually-driven networks. A surprising aspect of these findings is that large scale correlated networks are present very early in development, well before they can be engaged with visual stimuli and also prior to the elaboration of ordered long-range horizontal connectivity. Thus, it is unclear what circuit mechanisms are responsible for determining the organization of long-range correlated activity in the visual cortex.

To address this, we systematically examined the contribution of feed-forward inputs to the structure of correlated spontaneous activity in the ferret visual cortex. By using wide-field calcium imaging, we were able to capture spontaneous activity patterns spanning millimeters, and assay whether perturbations of feed-forward pathways alter its large-scale structure. Spontaneous retinal waves are prominent prior to eye-opening, and are thought to drive activity throughout the visual pathway. However, blocking retinal activity entirely with intra-ocular infusions of tetrodotoxin (TTX) had little effect on the both the frequency and spatial structure of correlated activity within the visual cortex in animals prior to eye opening, suggesting that retinal waves contribute little to the large-scale patterns of correlated activity in the early cortex. In addition to retinal waves, spontaneously active thalamocortical afferents could potentially drive correlated activity in the cortex. To address this, we infused the GABA agonist muscimol into

the ipsilateral lateral geniculate nucleus of the thalamus (LGN). Muscimol completely abolished visually-evoked orientation selective responses in the cortex, yet had only a modest effect on the spatial structure of spontaneous activity, which remained highly modular and continued to exhibit long-range organization. Taken together, these results suggest that the patterns of large-scale correlated spontaneous activity in the visual cortex are only weakly influenced by feed-forward drive, and rather reflect the organization of intracortical networks.

Disclosures: G.B. Smith: None. **D.E. Whitney:** None. **D. Fitzpatrick:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.10/GG31

Topic: D.07. Vision

Support: NIH Grant EY024071

Title: Whole cell recording of synaptic and intrinsic conductances in V1 of behaving monkeys

Authors: *B. LI, N. PRIEBE, E. SEIDEMANN
Univ. of Texas at Austin, Austin, TX

Abstract: We seek to understand how neurons integrate and transform synaptic inputs into patterns of spiking activity by using whole-cell recordings from V1 of behaving macaques. These membrane potential (Vm) records provide a perspective on both the network and intrinsic neuronal states that have not previously been available in primates. We hypothesized that hyperpolarizing neurons with current should increase visually-evoked responses given the associated changes in driving force for excitation and inhibition. Surprisingly, we found that responses to drifting gratings were largely invariant over a wide range of Vm. To examine which mechanisms could account for this invariance, we measured the membrane resistance (Rm) of cells at different resting potentials. We found that Rm increases with Vm, which has the effect of attenuating synaptic inputs at hyperpolarized potentials and enhancing inputs at more depolarized potentials. The increase in Rm with Vm reflects an intrinsic voltage-gated conductance that changes either when membrane potential is altered by current injection or by trial-to-trial voltage fluctuations. Finally, we explored how sensory stimulation alters both Rm and Vm using large and small visual stimuli. We found that small visual stimuli covering the classical receptive field depolarize neurons and evoke considerable decreases in Rm. As stimulus size increases, the Vm depolarization decreases, consistent with surround suppression. In concert with the reduced Vm depolarization, large stimuli evoked a smaller decline in resistance, indicating that surround suppression emerges from a reduction in overall synaptic input instead of additional synaptic inhibition. While visual stimulation generally caused a reduction in

membrane Rm that is proportional to the increase in Vm, trial-to-trial fluctuations in Rm were still positively correlated with trial-to-trial fluctuations in Vm, consistent with a voltage-gated intrinsic conductance. Overall, our results provide novel constraints to models of the intrinsic and synaptic conductances that underlie information processing by cortical neurons in behaving subjects.

Disclosures: B. Li: None. **N. Priebe:** None. **E. Seidemann:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.11/GG32

Topic: D.07. Vision

Support: NIH Grant

Title: The functional synaptic architecture of the receptive field surround of layer 2/3 pyramidal neurons in of tree shrew visual cortex

Authors: *K.-S. LEE, D. FITZPATRICK
Max Planck Florida Inst., Jupiter, FL

Abstract: The receptive field surround is the region of visual space that does not drive spiking responses but can exert a strong impact on the neuron's response to stimulation of the receptive field center. A major contributor to receptive field surround modulation is thought to be long-range horizontal connections that arise from layer 2/3 pyramidal cells. Previous studies have demonstrated that the horizontal network is arranged in a modular fashion that is correlated with the structure of the columnar orientation preference map, consistent with a contribution to iso-orientation tuned receptive field surround effects. However, how the horizontal network connects to its postsynaptic target and how it relates to the spatial extent of pyramidal cell dendritic arbors still remain unclear. In this study, we sparsely labeled neurons in visual cortex with GCaMP6s calcium indicator, and applied *in vivo* two-photon imaging to measure the receptive field center, and the tuning properties of individual dendritic spines exclusively responding to stimuli lying in regions of visual space at least 7.5° beyond the somatic receptive field center. Consistent with previous anatomical studies, our results provide support for an iso-orientation and co-axial bias of the synaptic inputs from the receptive field surround and add to this, synaptic specificity for absolute spatial phase, a property that is likely to enhance the contribution of contextual interactions to contour integration. Unexpectedly, we found that the distribution of synaptic inputs to the apical dendrites of layer 2/3 neurons is biased to the far surround, while synaptic inputs to the basal dendrites are biased to the receptive field center and nearby surround. Moreover, while there is no sign of a visuotopic map in the dendritic field, inputs from the

surround in the apical dendrite exhibit a clustered visuotopic arrangement. These results suggest that both the functional specificity of synaptic inputs and their spatial arrangement within the dendritic field contribute to receptive field surround modulation.

Disclosures: K. Lee: None. **D. Fitzpatrick:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.12/GG33

Topic: D.07. Vision

Support: Swiss National Science Foundation

HHMI

Title: Contextual modulation in visual cortex

Authors: *A. KELLER[1], M. S. CAUDILL[2], M. SCANZIANI[3]
[1]Physiol., UCSF, San Francisco, CA; [2]CNCB, Univ. California San Diego, La Jolla, CA; [3]Univ. of California, San Francisco, San Francisco, CA

Abstract: Sensory neurons are activated by stimuli and modulated by context. Typical examples of contextual modulation are surround suppression and facilitation in the visual system. Pyramidal cells in primary visual cortex (V1) are activated by patches of gratings in their receptive field and suppressed by the same gratings away from their receptive field, i.e. in their surround. In a different context, obtained simply by changing the orientation of the gratings in the surround, their responses are facilitated. The cellular and synaptic mechanisms underlying surround modulation are poorly understood. Here, we investigate surround modulation in pyramidal cells and three major subclasses of inhibitory cells of mouse V1: somatostatin-expressing (SOM), parvalbumin-expressing (PV), and vasoactive-intestinal-peptide-expressing neurons. We show that SOM, but not PV or VIP cells are facilitated by an iso-oriented surround and suppressed by a cross-oriented surround. That is, SOM cells show a response to the surround which is opposite to that of pyramidal cells. We aim to perturb individual subclasses of cells to establish the circuits for contextual modulation.

Disclosures: A. Keller: None. **M.S. Caudill:** None. **M. Scanziani:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.13/HH1

Topic: D.07. Vision

Support: HHMI

Gatsby Charitable Foundation

Title: The mechanism of direction selectivity in mouse visual cortex

Authors: A. D. LIEN, *M. SCANZIANI
Univ. of California, San Francisco, San Francisco, CA

Abstract: The ability to extract the direction of motion in visual scenes is essential for our representation of the environment. Visual cortex is one of the main stages in the mammalian nervous system where selectivity for direction of motion emerges de novo. Experiments and theories indicate that cortical neurons respond selectively to motion direction by combining inputs that provide information about distinct spatial locations with distinct time-delays. Despite the importance of this spatiotemporal offset for direction selectivity its origin and cellular mechanisms are not understood. Here we show that direction selective neurons in mouse visual cortex receive convergent input from thalamic neurons responding with distinct time-courses to stimuli in distinct locations. Integration of these spatiotemporally offset thalamic inputs provides cortical neurons with the primordial bias for direction selectivity. These data show how cortical neurons, by specifically combining the spatiotemporal response diversity of thalamic neurons extract fundamental features of the visual world.

Disclosures: A.D. Lien: None. **M. Scanziani:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

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Topic: D.07. Vision

Support: NIH Grant NS088906

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NIH Grant P30 EY013079

Title: Quantitative axonal synaptic ultrastructural analysis of macaque v1 from serial em sections

Authors: *V. GARCIA-MARIN, M. J. HAWKEN
Ctr. For Neural Science. New York Universty, New York, NY

Abstract: In cortex, synaptic boutons vary in size, composition, and number of synaptic contacts. We tested whether the distribution of sizes and categories of synaptic boutons was invariant across different layers of macaque V1. We used Focused Ion Beam/Scaning Electron Microscopy (FIB/SEM) to obtain serial images, ESPina (Morales et al., 2011) to quantify synapses, and AMIRA to reconstruct terminal boutons in 3D.
First, we determined that the synaptic density was 0.49, 0.75 and 0.66 synapses/μm^3 in layers 4Cα, 4Cβ and 2/3, respectively. Symmetric synapses represented 14% of the total population independent of layer. Asymmetric (A) boutons were assigned to four categories, according to whether there was a single (S) or multiple (M) postsynaptic densities (PSDs) and whether the bouton contained mitochondria (M+) or not (M-). Additionally, the bouton target was identified as a spine or dendrite. We found that for all layers the ASM- category was the most prevalent (52%, 62% and 60%, for 4Cα, 4Cβ and 2/3 respectively). The boutons establishing multiple synapses (AMM+) preferentially contact spines (91%, 86%, 85%, for 4Cα, 4Cβ and 2/3, respectively), whereas boutons making one synapse (both ASM+ and ASM-) tend to make fewer spine contacts (60%, 59%, 64% for ASM- and 66%, 60%, 74% for ASM+ in 4Cα, 4Cβ and 2/3, respectively).
Further, we made 3D reconstructions of individual boutons in 4Cα and 4Cβ to measure total volume, volume occupied by mitochondria, and number of PSDs. AMM+ boutons were, on average, 12 times larger than ASM- boutons (mean: 2.04 vs 0.17 μm^3). The volume occupied by mitochondria scaled linearly with bouton volume (r=0.97) and was on average 23.4% of the total volume (range, 14.5% to 36.9%). The number of synapses also scaled with bouton volume (r=0.78). In 4Cα, we reconstructed 18 boutons that made multiple synapses (72% with 2 contacts and 23% with 3 contacts), and in 4Cβ we reconstructed 32 boutons with multiple PSDs (50%, 38%, 6%, 3% and 3%, for 2, 3, 4, 5, and 6 synapses, respectively). In layer 2/3, the majority of the multiple boutons establish 2 synapses (91%) and only 9% establish 3 synapses.
Our results showed that the range of bouton sizes and the proportion of boutons in each category were similar in different cortical layers. This suggests that common general principles underlie the neuropil composition in different areas/layers of cortex. Furthermore, if the general size principle (Pierce & Lewin, 1994) holds for V1, this result implies equivalent ranges of synaptic strength in different layers.
Pierce JP, Lewin GR. 1994. Neurosc. 58:441-446;
Morales J et al. 2011. Front Neuroanat. 5:18

Disclosures: **V. Garcia-Marin:** None. **M.J. Hawken:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: D.07. Vision

Support: NIH grant - MH 93567

Title: Axonal innervation density predicts basal monoaminergic tone in macaque V1

Authors: ***N. J. WARD**, A. A. DISNEY
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Abstract: The monoaminergic systems exhibit widespread projections that locally influence the output of cortical circuits. One important assumption of neuroanatomical studies of monoaminergic systems is that their innervation patterns in cortex can be used as a basis for understanding their functions. This process of inferring function from neuroanatomy must be done with caution, and such inferences made from structural data must be strengthened by supporting functional evidence. Here we present preliminary evidence that monoaminergic innervation density in the primary visual cortex (V1) of the macaque is predictive of basal levels of released monoamines. In prior studies, the degree to which noradrenergic (NA), dopaminergic (DA), and serotonergic (5-HT) systems influence V1 circuitry *in vivo* has often been inferred using postmortem tissue metrics such as concentrations of these neurochemicals, degree of axonal innervation, and extent of receptor expression. Based on previous non-human primate studies, NA and 5-HT axons both exhibit more extensive innervation of V1 than DA axons. Likewise, measurements of postmortem concentrations of these molecules indicate 5-HT exhibits the highest levels while DA exhibits the lowest levels of the three molecules. In applying these data to functional models of these systems, a central concern is that we use measurements representative of *in vivo* basal levels. To address this in the present study, we used *in vivo* microdialysis to collect extracellular fluid from V1 of the awake, behaving macaque monkey. Within a collection session, a microdialysis probe was implanted in V1 and continuously perfused with artificial cerebrospinal fluid to collect samples. Concentrations of NA, DA, and 5-HT were measured from each sample using mass spectrometry. In line with previous observations, our data show that early in collection sessions there is a damage-related release of measured analytes. Samples collected after this release has leveled off show higher levels of 5-HT and NA when compared to DA. These data provide functional evidence that monoaminergic innervation patterns of local cortical circuitry can be predictive of basal levels of monoamines. Such measurements may be useful for examining the relative contribution of each molecule to basal monoaminergic tone across the entirety of the cortex. The ability to pair

measured levels of monoamines with knowledge of circuit features such as receptor and degradation machinery expression across the circuit will help develop a functional understanding of how these monoaminergic systems influence V1.

Disclosures: N.J. Ward: None. **A.A. Disney:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

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Topic: D.07. Vision

Support: NIH/NIMH Grant R01 MH 102365-04

NIH/NEI Grant R01 EY 022951-04

Title: Laminar organization of functional sub-networks in the primary visual cortex of awake mice

Authors: *Q. PERRENOUD, J. A. CARDIN
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Abstract: The cerebral cortex is the principal substrate of cognitive activity in the mammalian brain. Cortical function is impaired in major psychiatric diseases such as schizophrenia and Autism Spectrum Disorders. The cortical network subdivides in 6 layers whose anatomical architecture has been well described. However the role that each layer plays in cortical processing remains poorly understood. In the canonical hierarchical model of cortical processing, activity would proceed from layer 4 to layers 2/3 to the infragranular layers. However, recent evidence suggests the possibility of multiple non-hierarchical cortical sub-networks. In order to better understand laminar interactions within the cortical column, we devised an integrated approach combining acute multi-contact laminar silicon probe recordings with patch clamp recordings in the primary visual cortex (V1) of awake head-fixed mice running freely on a wheel. Neurons were recorded in layers 2 to 5 during simultaneous monitoring of pupil diameter, a biomarker of arousal, and presentation of visual stimuli. Spike Triggered Averaging (STA) combined with Current Source Density (CSD) analysis indicates that the recruitment of individual cortical neurons coincides with the activation of sub-networks composed of particular sub-layers of layers 2-3, 4 and 5. The recruitment of these networks is differentially affected by locomotion, arousal and visual processing. Taken together, these data challenge the notion that layers 2-3, 4 and 5 form homogenous functional entities. Rather they suggest the existence of functional modules which are distributed across cortical layers and represent parallel streams of network operation.

Disclosures: **Q. Perrenoud:** A. Employment/Salary (full or part-time):; Yale University. **J.A. Cardin:** A. Employment/Salary (full or part-time):; Yale University.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.17/HH5

Topic: D.07. Vision

Title: Spike time reliability across populations in mouse LGN and V1

Authors: *D. J. DENMAN[1], G. K. OCKER[2], S. DURAND[1], Y. N. BILLEH[2], N. W. GOUWENS[1], M. A. BUICE[1], S. E. DEVRIES[1], R. REID[2]
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: The mammalian visual system builds and transforms representations of the outside world through the concerted activity of populations of neurons. Given specific wiring and complex dendritic properties, a number of plausible coding strategies, from linear rate coding to complex spike timing codes, could be supported. While much information can be extracted using rate codes, the dynamics of visual behavioral performance suggest at least some form of the more information-rich coding should be present. For example, models of neural coding that rely on precise spike times have long been posited, but a lack of empirical data about the single neuron spike times in population activity has left these ideas largely untested. Here, we describe the responses to repeated presentations of rapidly varying stimuli across populations of 30 - 100 simultaneously recorded neurons in primary visual cortex (V1) and lateral geniculate nucleus (LGN) of awake, passively-viewing mice using high-density electrophysiology. For each structure, we measure both reproducibility of spike trains across trials and the variability of latency (a.k.a., precision) across response events for single cells. While single cells were most precise in LGN, followed by layer 4 of V1, entire spike train reproducibility was not significantly different across LGN or cortical layers. To address the plausibility spike time-based representations in these populations, we measured pairwise correlation, across cells, in the latency of response events. This correlated latency was non-zero, supporting the possibility of representation via spike time. Finally, we extended this analysis to the entirety of the simultaneously recorded populations, comparing the the mean precision and reproducibility of single neurons to that of the of the entire recorded ensemble spike train. Population response was significantly more reliable than single cells, suggesting that spike-time based representation is more plausible in cortical populations than single cell measurements might suggest.

Disclosures: **D.J. Denman:** None. **G.K. Ocker:** None. **S. Durand:** None. **Y.N. Billeh:** None. **N.W. Gouwens:** None. **M.A. Buice:** None. **S.E. DeVries:** None. **R. Reid:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Topic: D.07. Vision

Support: Branco Weiss-Society in Science grant

HFSP Fellowship

Title: Diverse and dynamic global affiliations of cortical neurons

Authors: *K. CLANCY[1], I. ORSOLIC[2], T. MRSIC-FLOGEL[2]
[1]Biozentrum, Univ. of Basel, Basel, Switzerland; [2]Univ. of Basel, Basel, Switzerland

Abstract: Neurons in the neocortex, responsible for our most complex behaviors, are richly interconnected within distributed associative networks. Each principal neuron receives input from and provides input to both local and long-range partners. But how cortical neurons within an area associate functionally with local and global network activity is not well understood. We determined the coupling of cortical neurons to cortex-wide activity patterns by recording spiking from populations of neurons in visual and retrosplenial cortex while imaging calcium activity across the dorsal cortical surface. We found that individual neurons were associated with diverse cortex-wide activity patterns; while some fired predominantly when the local network was active, others were more strongly coupled to distal cortical regions. Global affiliations of individual neurons were predicted by how strongly they correlated with the local spiking network. These affiliations shifted with the animal's behavioral state in a region dependent-manner, suggesting that individual neurons may dynamically participate in global associative networks.

Disclosures: K. Clancy: None. **I. Orsolic:** None. **T. Mrsic-Flogel:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Topic: D.07. Vision

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Title: Identification of sequential activity patterns in cortical ensembles using probabilistic graphical models

Authors: *S. HAN[1], L. CARRILLO-REID[1], *J. SHOR[2], T. JEBARA[2], R. YUSTE[1]
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Abstract: Sequential activity patterns have been proposed as a general mechanism for a wide variety of physiological behaviors in different brain areas. However, how the coordinated activity of neurons firing in synchrony and organized in temporal sequences relates to the network properties of cortical microcircuits has been difficult to elucidate. It has been shown that cortical ensembles in layer 2/3 of primary visual cortex fire synchronously representing different visual stimuli. We recently developed a method using probabilistic graphical models to characterize the network properties of cortical microcircuits allowing the identification of cortical ensembles and the prediction of visual stimuli from two-photon calcium imaging population data. We now extend our method to study sequential activity patterns of cortical ensembles. Using simultaneous two-photon imaging and two-photon optogenetics we show that probabilistic graphical models could be also used to investigate the temporal reconfiguration of cortical microcircuits induced by sequential activity patterns. This method opens the possibility to understand if the optogenetic imprinting of sequential activity patterns with single cell resolution modulates physiological behaviors.

Disclosures: S. Han: None. **L. Carrillo-Reid:** None. **J. Shor:** None. **T. Jebara:** None. **R. Yuste:** None.

Poster

148. Visual Cortex: Circuits and Populations

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NIMH (R01MH101218, R01MH100561)

Army Research Office W911NF-12-1-0594 (MURI)

Title: Clustered modular organization of neuronal ensembles in mouse visual cortex

Authors: *W. FANG, R. YUSTE
Columbia Univ., New York, NY

Abstract: The spatiotemporally orchestrated activation of groups of neuronal ensembles likely underlies cognition and forms the neural basis of behavior. Ensembles can spontaneously coordinate their activities via recurrent neuronal connections and also be recruited by sensory stimulation, and therefore are proposed as basic circuit building blocks of neural networks. However, their structural and functional organization and construction remain poorly understood. With two-photon calcium imaging of neurons in adult mouse primary visual neocortex, we find that stable neuronal ensembles exhibit functional selectivity and can be invoked by specific visual stimuli. Moreover, these ensembles are not simply gathering of neurons with similar orientation preference and scattered in their location, but are highly inter-connected and spatially clustered. Importantly, the spatial segregation of ensembles is related to their functional separation in discriminating different orientations. Furthermore, by comparing neuronal ensembles in dark-rearing mice to those in wild type animals, we find that visual experience does not significantly affect spatial segregation of ensembles, but instead enhances their functional separation. Our results indicate that neuronal ensembles are structural and functional cortical modules, and suggest that, while intrinsic self-organizing mechanisms shape the structural segmentation of ensembles, experience sculpts their functional specificity.

Disclosures: W. Fang: None. **R. Yuste:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 148.21/HH9

Topic: D.07. Vision

Title: Linking V1 spatial frequency and orientation population responses to perception

Authors: *N. JU[1], Y. SHAO[1], S. GUAN[2], S. TANG[1], L. TAO[1], C. YU[2]
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Abstract: Spatial frequency and orientation processing is the basis of form perception. Psychophysical theories assume the existence of independent low, medium, and high spatial frequency channels. The responses of these channels are collectively responsible for the formation of the contrast sensitivity functions that show maximal contrast sensitivity at medium frequencies, slightly less sensitivity at lower frequencies, and rapidly reduced sensitivity at high frequencies up to a cut-off frequency with zero sensitivity. However, a systematic survey of

neural basis of contrast sensitivity functions has been lacking. Here we use two-photon calcium (GCaMP5) imaging of awake, fixating monkey to investigate the individual and population spatial frequency responses of layers 2 and 3 V1 neurons (at depths of 150 um and 300 um, respectively). The visual stimulus consists of Gabor gratings at 12 orientations (-45-120 deg), 6 spatial frequencies (0.25-8 cpd) at 90% contrast and drifting at 2 cycles/sec. We recorded from 1194 and 1475 neurons (orientation OSI > 0.5, ANOVA $p < 0.05$) at two sites (both within a window of 850x850 um at 3-deg parafovea). The results show that the majority of the neurons (80% in both layers 2 and 3) have optimal spatial frequencies between 1-4 cpd, while a significantly smaller subpopulation of neurons (9% in layer 2, 5% in layer 3) have preferred spatial frequency less than 1 cpd. However, the summed population responses resemble typical contrast sensitivity functions, with the lower frequency portion of the summed responses mainly coming from the medium frequency neurons (with preferred frequency at ~1-4 cpd). Furthermore, both layers 2 and 3 have highly orientation selective neurons, with ~40% of the neurons having orientation bandwidths (half-width at half maximum) less than 30 degrees and ~9% less than 15 degrees. These neurons are likely to be the main contributors to fine orientation perception. On the other hand, neurons with broader orientation tuning bandwidths may contribute to higher-order visual stimuli, such as the orientation of second-order gratings.

Disclosures: **N. Ju:** None. **Y. Shao:** None. **S. Guan:** None. **S. Tang:** None. **L. Tao:** None. **C. Yu:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Topic: D.07. Vision

Support: MRC BH071485

Autonomous Province of Trento (“Grandi Progetti 2012,” “ATTEND”)

Title: Perceptual learning induced changes to information content of V4 neuronal populations

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Abstract: Perceptual learning describes improved sensory discrimination abilities that occur with training throughout life. Perceptual improvements in simple visual discrimination tasks co-occur with altered neuronal tuning in various areas of the visual cortex. Moreover, it may be due

to reduction of internal noise, but evidence is limited due to a lack of data that is recorded simultaneously from multiple channels during learning.
To address this, we recorded from chronically implanted multi-electrode arrays from area V4 in two macaque monkeys, while they were trained in a contrast discrimination task (two-interval 2AFC task of reporting whether a test stimulus was of higher or lower contrast than a sample stimulus). Recordings were performed from the beginning of training, until performance plateaued (after about 20-25 training days).
We used Fisher information to quantify how well an ideal observer could discriminate between different sample-test contrasts based on activity obtained from a given channel. Distributions of information content across the population were well approximated by an exponential function: most channels encoded relatively little information, but a few channels encoded comparatively large amounts. Information content for early vs. late training days showed the largest absolute differences for channels that encoded relatively large amounts of information. Nevertheless, increases in Fisher information were not restricted to channels with high information coding capacities at the beginning of training. In fact, Fisher information relative increases were larger in channels that encoded relatively little information at the start of training.
We found that training reduced noise correlations. To analyse their contribution to increased population information content with training, we calculated population Fisher information for different subpopulation sizes. We sequentially added channels (rank ordered for Fisher information values) to the subpopulation, and analysed the data and shuffled data destroying correlations. Population information content was higher during the late training period than during the early training period. The information increase as channels were added was gradually getting smaller, owing in part to the differing amounts of information present in individual channels, but also to the signal and noise correlations that were present between channels. Most of the increases in population coding stemmed from increases in single channel coding. Noise correlation reductions benefitted primarily the neuronal subpopulations that conveyed larger amounts of information.

Disclosures: **A. Thiele:** None. **X. Chen:** None. **M. Sanayei:** None. **D. Chicharro:** None. **S. Panzeri:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Support: NSC 101-2321-B-002-078

NSC 102-2321-B-002-059

MOST 103-2321-B-002-028

MOST 104-2320-B-002-065-MY3

Title: Synchronous firing of black-dominant and white-dominant cell pairs in macaque V1

Authors: *W. TAI[1], H.-Y. WU[1], W.-M. HUANG[1], Y.-C. PEI[2], C.-I. YEH[1,3,4]
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Abstract: Previous studies have shown that black-dominant neurons outnumber white-dominant neurons in the primary visual cortex V1 in many species. The black-over-white bias may serve as the neural substrate for better and faster processing of black than white objects. One possible neural mechanism for the ample black preference is through recurrent connections in the superficial layer of V1 (Xing et al 2010) - the black-dominant signal is more sustained for the multi-unit activity than for the local field potential. Based on the finding, we hypothesized that the strength of synchronous firing between black-dominant neurons should be stronger than that between white-dominant neurons. Here we used a multi-electrode matrix (8 probes x 8 sites, 200 um spacing, Neuronexus) to simultaneously record from multiple neurons in different cortical layers of macaque V1. The receptive field measured with sparse noise by reverse correlation (Jones & Palmer 1987) was used to determine a cell's response bias (black or white dominant, Yeh et al 2009). The number of cell pairs is 564 for sparse noise and 323 for dense noise. We quantified the strength of synchronous firing of a cell pair as the peak amplitude minus the baseline amplitude (average between -100 and -60ms and between 60 and 100ms) of the cross-correlogram. In consistant with pervious finding. there were more black-dominant cells than white-dominant cells with sparse noise. For both black- and white-dominant cell pairs, the correlation strength was negatively correlated with the distance of a cell pair ($r=-0.364$, $p<.001$, Pearson correlation). Moreover, the strength of the synchronous firing is also modulated by the stimulus. In comparison with white-dominant cell pairs, the average correlation strength of black-dominant cell pairs tended to be smaller with sparse noise, but tended to be larger with dense noise (a binary white noise generated by m-sequence, Reid et al 1997). The surprising result that weaker correlation strength in black-dominant cell pairs under sparse noise is probably related to the finding that dark stimuli generate higher sustained spike-firing rate response than bright stimuli (Xing et al, 2014). Overall, these results indicate that the synchronous firing of V1 cell pairs may serve to indicate the stimulus statistics.

Disclosures: **W. Tai:** None. **H. Wu:** None. **W. Huang:** None. **Y. Pei:** None. **C. Yeh:** None.

Poster

148. Visual Cortex: Circuits and Populations

Location: Halls A-C

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Topic: D.07. Vision

Support: Wellcome Trust 095668

Wellcome Trust 095669

Simons Foundation (SCGB 325512)

Gatsby Charitable Foundation

Title: Recordings of ~10,000 excitatory and inhibitory neurons reveal high-dimensional representations of sensory stimuli and behavioral state in cortex

Authors: *C. STRINGER[1], M. PACHITARIU[2], S. SCHRÖDER[2], C. REDDY[2], M. CARANDINI[2], K. D. HARRIS[2]
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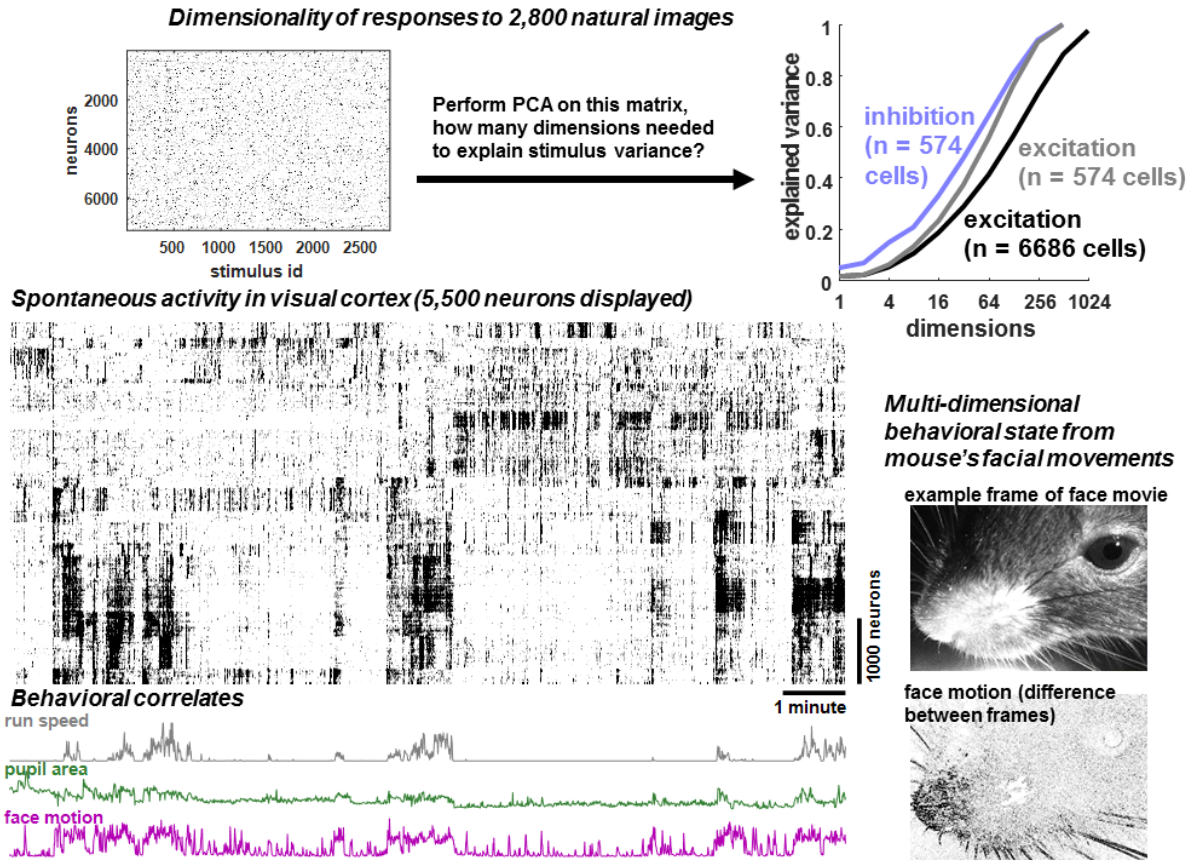
Abstract: To process sensory information efficiently, biological and artificial neural systems require a high-dimensional code. However, multi-neuron recordings have suggested only a few dimensions of activity, potentially due to limitations of the number of recorded neurons and presented stimuli.
We removed these limitations by simultaneously recording from ~10,000 neurons in visual cortex of awake mice using two photon calcium imaging, and by presenting 2,800 natural image stimuli. The neurons spanned layers 2-4 in a volume of 0.3 mm^3, and included a subpopulation of ~700 inhibitory (GAD+) neurons labelled by td-Tomato. Cell detection and signal extraction were performed by Suite2p (Pachitariu et al, bioRxiv 2016).
Population responses spanned a space of at least thousands of dimensions, with dimensionality increasing linearly with the number of presented natural images (at a rate of ~0.3 dimensions/image).
The dimensionality of spontaneous activity was lower, consisting of ~50 significant dimensions, which were spatially interspersed in the volume. This spontaneous activity continued uninterrupted during sensory stimulation, and was unrelated to the sensory-evoked activity. Instead, the spontaneous activity patterns were related to ~15 dimensions of behavioral state as determined from movies of the face, pupil and whiskers of the mouse.
In response to natural images, inhibitory populations spanned as many dimensions as a size-matched population of excitatory neurons. However, while excitatory neurons responded sparsely to stimuli, inhibitory neurons responded densely. During spontaneous activity,

inhibitory neuron activity tracked excitatory neuron activity across dozens of dimensions, and covaried with the same ~15 of dimensions of behavioral state as excitatory neurons.
We conclude that visually driven activity is high-dimensional in both excitatory and inhibitory cortical populations, suggesting specificity in excitatory-inhibitory connectivity. Spontaneous activity, however, is lower dimensional and covaries with measures of behavioral state.



Disclosures: **C. Stringer:** None. **M. Pachitariu:** None. **S. Schröder:** None. **C. Reddy:** None. **M. Carandini:** None. **K.D. Harris:** None.

Poster

148. Visual Cortex: Circuits and Populations

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R01EY011787

DARPA SIMPLEX N66001-15-C-4032

ARO W911NF-12-1-0594 (MURI)

Title: Sequential activation of neuronal ensembles in mouse primary visual cortex

Authors: *A. AKROUH[1], L. CARRILLO-REID[1], S. HAN[1], R. YUSTE[2]
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Abstract: Changes in visual stimuli generate coherent activation of groups of neurons (ensembles) in mouse primary visual cortex (V1). Interestingly, ensemble activity also occurs spontaneously in the absence of visual stimuli, suggesting that cortical microcircuits generate an internal representation of visual experience. Consequently, training to a new visual stimulus could reconfigure the patterns of cortical ensembles, conferring circuits with computational features such as pattern completion. Yet, whether specific activity sequences of cortical ensembles can be artificially programed in the absence of visual stimuli remains unknown. Here we use in vivo two-photon calcium imaging in awake mice to record spontaneous and visually evoked activity in V1. Using a probabilistic graphical model, we identify naturally occurring cortical ensembles and their temporal structure and find that both visually evoked and spontaneous ensembles occur in characteristic temporal sequences. We then use targeted optogenetic activation of individual cells and of groups of cells to program artificial sequential activity patterns and to test whether they persist spontaneously. Further experiments aim to entrain cortical ensembles to specific visual stimuli and to test how sequential ensemble activation modulates visually guided behavior.

Disclosures: **A. Akrouh:** None. **L. Carrillo-Reid:** None. **S. Han:** None. **R. Yuste:** None.

Poster

148. Visual Cortex: Circuits and Populations

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NDSEG

RK Mellon

Title: The relationship between pairwise correlation and dimensionality reduction

Authors: *R. MORINA[1], B. R. COWLEY[2], M. A. SMITH[3], B. M. YU[2]
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Abstract: Spike count correlation, also known as “noise correlation”, has been used extensively to characterize the interaction between pairs of neurons. With the advent of multi-electrode array recordings, dimensionality reduction is being increasingly used to study the interaction of many neurons simultaneously. Here, we explore how the insights obtained from pairwise correlation metrics relate to those from dimensionality reduction. We first used simulated data to systematically alter dimensionality reduction metrics and observed the related changes in pairwise correlation metrics. We then used population recordings in macaque visual cortex to understand how the relationships we discovered with simulated data apply to real data and under what conditions these relationships hold. We further investigated how well pairwise correlation metrics can predict dimensionality reduction metrics. We found that, for a given population of neurons, there is a systematic relationship between the spike count correlation distribution (created from all pairs of neurons) and the shared co-fluctuation patterns across the population, identified with factor analysis. This relationship depends on the number of shared co-fluctuation patterns identified, as well as the strength of these patterns. These findings help bridge studies that utilize these different approaches for analyzing neural population activity.

Disclosures: R. Morina: None. **B.R. Cowley:** None. **M.A. Smith:** None. **B.M. Yu:** None.

Poster

148. Visual Cortex: Circuits and Populations

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Topic: D.07. Vision

Support: Whitehall Foundation 20121221

NSF CRCNS 1308159

NIH R00 MH104259

Title: Network criticality in mouse visual cortex coincides with high single-neuron response variability, but low correlated variability

Authors: *J. XIA[1], P. T. O'NEILL[2], M. J. GOARD[2], R. WESSEL[1]
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Abstract: Many, but not all, cortical circuits operate near criticality, which is a network state that resides at the boundary between order (large-scale activity) and disorder (small-scale activity). Single-neuron sensory responses in cerebral cortex are highly variable across stimulus presentations and this trial-to-trial variability can be correlated across pairs of neurons. These two seemingly separate observations at the network and single-neuron raise an important question: To what extent are the network state and single-neuron response properties related in cortical circuits?
To address this question, we performed two-photon calcium imaging of layer 2/3 pyramidal neurons in primary visual cortex of head-fixed, behaving mice during visual stimulation (low-pass filtered Gaussian noise and natural movies). For each mouse and visual stimulation condition, we obtained the DF/F recordings from approximately 300 within a 690 micron field. We inferred spike trains from the DF/F recordings. We analyzed the inferred spike train population activity with respect to spatiotemporal coordination using the concept of neuronal avalanches, which are cascades of contiguous spikes within the population of imaged neurons. From the single-neuron DF/F recordings, we analyzed the trial-to-trial response variability and its correlation across pairs of neurons for repeated presentations of visual stimuli. These analyses of population and single neurons revealed two important features.
First, the observed cortical circuits operated at criticality during visual stimulation. Both the size and the duration distributions of the neuronal avalanches followed power laws. Further, the exponents of the two distributions satisfied the scaling relation; a more stringent test of criticality than power law analysis alone.
Second, single-neuron DF/F responses to repeated visual stimuli were highly variable. The average correlation coefficients of DF/F recordings for pairs of trials were broadly distributed across neurons with a median of approximately 0.35. Furthermore, this trial-to-trial response variability was weakly correlated across pairs of neurons. In addition, correlated variability ("noise correlation") changed after movie onset.
In conclusion, these results show that L2/3 network criticality coincides with high single-neuron response variability and low correlated variability in visual cortex and that neocortical circuits reorganize during sensory processing. We are presently extending these studies to L4 and L5.

Disclosures: J. Xia: None. **P.T. O'Neill:** None. **M.J. Goard:** None. **R. Wessel:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

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Program#/Poster#: 149.01/HH16

Topic: D.07. Vision

Support: Israel Science Foundation 211/15

Title: Long range neural inhibition during visual selection process in the archerfish

Authors: S. VOLOTSKY[1], E. VINEPINSKY[2], O. DONCHIN[1], *R. SEGEV[3]
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Abstract: The archerfish, unique in its ability to hunt insects above water level by shooting a jet of water at the insect, operates in a complex visual environment with multiple potential targets. The fish needs to quickly prioritize some stimuli over others and to focus attention on a specific target. In some animals, global inhibition was found to serve as the mechanism for such a selection. Specifically, due to global inhibition, a potential target outside a neuron's receptive field suppresses the activity that is elicited by another potential target within the receptive field. We tested whether a similar mechanism operates in the archerfish. We recorded extracellular activity of neurons in the optic tectum while presenting a target stimulus inside the receptive field and a competing stimulus outside the receptive field. We held features of the target constant while varying the size, speed, and distance from the receptive field of the competing stimulus. We found that most cells exhibit global inhibition. That is, the competing stimulus depressed the firing rate significantly. In some neurons, this effect was dependent on the features of the competing stimulus. Our findings indicate that the optic tectum plays a crucial role in target selection process in the archerfish.

Disclosures: S. Volotsky: None. **E. Vinepinsky:** None. **O. Donchin:** None. **R. Segev:** None.

Poster

149. Spatial and Feature-Based Attention

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Support: NEI Intramural Research program

Title: Involvement of striatum in selective visual attention in mice

Authors: *L. WANG[1], R. J. KRAUZLIS[2]
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Abstract: Mice have been a useful model for studying neural circuit mechanisms for a wide range of behaviors, thanks to the availability of genetic tools. Here we developed a visual selective attention paradigm in mice, and tested the role of a subpopulation of neurons in the

striatum.
Mice were trained on a visual orientation-change detection task. Head-fixed and running mice viewed a pair of vertical gratings, each centered in the left or right visual field. On each trial, if either grating changed its orientation, mice needed to contact a lick spout to get a reward. In separate blocks, mice were either given a spatial cue or no cue. On cued blocks, a spatial cue at the beginning of the trial indicated the location of the possible change (50% probability); on no-cue blocks, an orientation change was possible on either side (each 25% probability). Trials with cues on the same side were organized as blocks. Mice (n=14) showed robust cueing effects, which consisted of increases in sensitivity (1.74±0.12, mean±SEM, cued; 1.18±0.12, no cue, $p<0.001$, paired sample t-test), decreases in criterion (0.39±0.06, cued; 0.70±0.09, no cue, $p<0.001$), and decreases in reaction time (0.46±0.008s, cued; 0.49±0.01s, no cue, $p<0.001$).
We then tested the possible role of the striatum in the control of selective attention. Using Drd1a-Cre mice (n=8) and a Cre-dependent AAV2-DIO-ChR2 virus, we stimulated medium spiny neurons in the direct pathway in the dorsomedial striatum during the task. In 50% of trials, we applied unilateral optogenetic stimulation (0.1-0.8mW) through an implanted optic fiber. On cued blocks when the visual event was expected on the contralateral side, striatal stimulation caused a large reduction in decision criterion (-0.85±0.07); for expected ipsilateral events, the effect was smaller (-0.21±0.07). On no-cue blocks,
when events on both sides were equally likely, striatal stimulation caused an intermediate reduction (-0.71±0.12, contralateral; -0.64±0.10, ipsilateral, $p=0.19$).
Together, our results demonstrate that mice can be a robust animal model for studying visual selective attention, and are consistent with a model in which 1) dorsomedial striatum is involved in flexible decision-making including spatial priors, 2) striatal circuits preferentially process contralateral visual events, and 3) striatal direct pathway activation introduces an additive bias before the decision threshold is applied.

Disclosures: L. Wang: None. **R.J. Krauzlis:** None.

Poster

149. Spatial and Feature-Based Attention

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Program#/Poster#: 149.03/HH18

Topic: D.07. Vision

Title: Optogenetic inhibition of projections to area MT reveal a causal role of the FEF in the attentional modulation of visual cortex in non-human primates

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Abstract: Spatial visual attention modulates sensory responses in primate visual cortex. Specifically, the response to stimuli in the receptive field of a given neuron is enhanced when covert spatial attention is directed into the receptive field, rather than elsewhere. Microstimulation and inactivation studies suggest that the frontal eye field (FEF) plays a pivotal role in this top-down gain modulation of bottom-up sensory responses. To determine whether FEF evokes attentional gain changes via its direct axonal inputs to these areas we used optogenetics to inhibit the presynaptic terminals of FEF axons projecting to extrastriate visual area MT. If these FEF projections are causal for the MT response modulation by spatial attention, optogenetic stimulation in MT should specifically decrease attentional effects, without systematically influencing sensory responses.
We infused a viral vector (AAV5-αCaMKII-eNpHR3.0-mCherry) into the left FEF of one rhesus macaque using multiple injections. Several months after the injections we recorded single cell activity in area MT of the left hemisphere while the monkey was conducting a spatial attention task. Two moving random dot pattern (RDPs) were presented, one placed in the receptive field (RF) of the recorded neurons, the second in the opposite visual hemifield. At the beginning of each trial a cue identified the target RDP. The animal had to report a direction change in the target while ignoring direction changes in the other RDP. This generated two behavioral conditions with identical visual stimulation but where the stimulus in the RF was either attended or unattended.
For the recordings an electrode and an optical fiber were lowered into MT with an inter-tip distance of ~500µm. Trials with and without optical stimulation (594 nm) were randomly interleaved, and we stimulated with a continuous laser pulse of 700ms during the sustained response of MT neurons to the visual stimulation.
Optical stimulation reduced attentional modulation significantly within the stimulation period, predominantly by reducing the attentional response enhancement to the stimulus, rather than by affecting the response to the unattended stimulus. Our results indicate that the direct projection from area FEF to extrastriate cortex plays a causal role in the enhancement of neuronal responses by covert spatial attention in these areas.

Disclosures: **J. Hüer:** None. **M.G. Fortuna:** None. **H. Guo:** None. **L.T. Schiller:** None. **A. Gail:** None. **J. Gruber:** None. **H. Scherberger:** None. **J.F. Staiger:** None. **S. Treue:** None.

Poster

149. Spatial and Feature-Based Attention

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Simons Foundation

Sloan Foundation

Whitehall Foundation

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Klingenstein-Simons Fund

Title: Do spike count correlations in visual cortex limit perception? Evidence from attention and perceptual learning

Authors: *A. M. NI, D. A. RUFF, J. J. ALBERTS, J. SYMMONDS, M. R. COHEN
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Abstract: The correlated variability in the trial-to-trial responses of pairs of neurons (termed spike count correlations or r_{SC}) may limit perceptual performance. Many studies have reported task-related changes in spike count correlations. One possibility is that these changes might increase the information encoded by the neuronal population. However, correlated variability is low dimensional and optimal decoders would only be affected by correlations that lie along the dimensions in population space that encode the task-relevant stimulus feature. And, as animals and humans appear to not be optimal decoders, the importance of correlated variability depends more on whether correlations lie along the dimensions in neuronal population space that guide behavior. Here, we tested whether correlated variability lies along the axis in population space that best predicts monkeys' choices in a behavioral task designed to track both short-term and long-term changes in perceptual performance. We implanted two rhesus monkeys with microelectrode arrays in visual area V4. We then recorded the activity of neuronal populations while the monkeys practiced an orientation change-detection task that manipulated spatial attention. For any given orientation change, the monkey could either respond to the orientation change (correct trial) or not (incorrect trial). Attention was associated with improved perceptual performance within individual experimental sessions, while perceptual learning was associated with slow improvements in performance across many experimental sessions. Improvements in perceptual performance were associated with the same amount of change in correlated variability, whether those changes occurred quickly with attention or slowly with learning. We tested whether correlated variability accounts for choice-predictive activity in the recorded populations of neurons on a trial-by-trial basis in multiple ways. We used principal component analysis (PCA) to find the single dimension of population activity that accounts for the most correlated variability. Projections onto this dimension represent a single trial measurement of shared variability. We found that these trial-by-trial estimates of correlated variability were: 1) consistently different on correct and incorrect trials, and 2) correlated with projections onto the

axis in population space that best predicts the monkey's choices (found using a method by Haefner et al., 2013). These population decoding methods can be used to understand the relative importance of the information encoded by sensory populations and how that information is decoded for guiding performance on perceptual tasks.

Disclosures: A.M. Ni: None. **D.A. Ruff:** None. **J.J. Alberts:** None. **J. Symmonds:** None. **M.R. Cohen:** None.

Poster

149. Spatial and Feature-Based Attention

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McKnight Scholar Award

Title: Investigating the effects of attention and adaptation on the neuronal population representation of contrast

Authors: *D. A. RUFF, J. J. ALBERTS, J. SYMMONDS, M. R. COHEN
Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Many sensory and cognitive processes affect perception and also multiplicatively scale (or change the gain of) the responses of sensory neurons. This observation has raised the possibility that many of these processes share a common mechanism. In vision, two examples of such processes are visual attention, which improves perception of attended stimuli, and adaptation, in which neuronal responses and percepts are changed after repeated presentations of an identical visual stimulus. Attention has been hypothesized to improve perception by making stimuli look as if they have higher contrast. To test this hypothesis and quantitatively compare the effects of attention and adaptation, we measured how populations of neurons in visual area V4 encode stimulus contrast in different task conditions. While two monkeys performed a

detection task that allowed us to manipulate attention, adaptation, and the contrast of visual stimuli, we recorded simultaneously from several dozen neurons in area V4. We identified subsets of neuronal population response space along which stimulus contrast is encoded and measured how attention and adaptation affected the mean and variance of an estimate of stimulus contrast that was based on the population's activity. Consistent with the idea that attention increases perceived contrast, we found that attention is associated with population representations of contrast that have a higher mean and a lower variance estimate. However, adaptation was associated with both a decrease in the mean and in the variance of the decoded contrast estimate, suggesting that adaptation reduces apparent contrast but also decreases variability in the contrast estimate. These results suggest that attention and adaptation are associated with different changes in how populations of V4 neurons represent contrast and, more generally, that the responses of simultaneously recorded neuronal populations can be used to compare the mechanisms underlying sensory and cognitive processes.

Disclosures: D.A. Ruff: None. **J.J. Alberts:** None. **J. Symmonds:** None. **M.R. Cohen:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 149.06/HH21

Topic: D.07. Vision

Support: NIH Grant EY017921

Title: Effects of prefrontal cortex inactivation on feature and spatial attention in area V4

Authors: *N. P. BICHOT, A. GHADOOSHAHY, R. XU, M. L. WILLIAMS, R. DESIMONE
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Abstract: We have previously shown that neural signals in the ventral pre-arcuate (VPA) region of the prefrontal cortex (PFC) play an important role in feature-based visual selection (Bichot et al., 2015). Based on the strength and timecourse of attentional effects, we surmised that feature attention signals in VPA are the source of the priority maps observed in the frontal eye field (FEF), and that FEF in turn modulates the activity of neurons in visual cortical areas like V4 (Zhou and Desimone, 2011) and inferotemporal cortex (Bichot et al., 2015). Consistent with this hypothesis, we showed that inactivation of VPA impairs search performance and eliminates feature-based, but not spatial, attentional effects in FEF. If indeed VPA is a main source of feature-based attention effects, then inactivation of this region should also lead to a decrease of feature-based attentional modulation in visual cortex. We tested this hypothesis by measuring attentional effects in area V4 with or without inactivation of VPA.
Two male macaque monkeys were trained to perform a free-viewing visual search task. After

fixating a central fixation spot, monkeys were presented with a central cue showing the target stimulus for that trial, and after a delay period the search array was presented. Monkeys had 5 s from array onset to find the target, and no constraints were placed on their eye movements so that they could conduct the search naturally. When the monkeys found the target, they fixated it for 800 ms continuously. Stimuli were conjunctions of 7 colors and 7 shapes, and were positioned at 20 locations selected based on the receptive field (RF) locations of the recorded neurons. The target location and identity were chosen pseudo-randomly from trial to trial. For inactivation sessions, injections of 1 ul of muscimol (5ug/ul) were made at three depths and two locations within VPA. Feature-based attention was quantified as the difference in neural responses to the target vs. a distractor in the RF when saccades were made to a location outside the RF. Spatial attention was quantified as the difference in neural responses when the animals made a saccade to a stimulus in the RF vs. one outside the RF. Following VPA inactivation, feature-based attentional modulation in V4 was eliminated prior to the first saccade, and significantly reduced prior to subsequent saccades. Spatial attention on the other hand was not significantly affected prior to the first saccade, but it was somewhat reduced on subsequent saccades. Altogether, these results support the hypothesis that prefrontal cortex provides a top-down attentional bias toward target features that modulates sensory processing in V4 and other visual cortical areas.

Disclosures: **N.P. Bichot:** None. **A. Ghadooshahy:** None. **R. Xu:** None. **M.L. Williams:** None. **R. Desimone:** None.

Poster

149. Spatial and Feature-Based Attention

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Topic: D.07. Vision

Support: Whitehall 2014-5-18

NSF BCS143221

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NIH R01EY026924

Title: Interactions between top-down and bottom-up input alter noise correlations in extrastriate cortex

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Abstract: Changes in the correlations between neurons are powerful mechanisms for altering visual cortical representations. Previous studies of the effect of top-down signals, such as attention, on correlations in visual cortex have all examined changes in visually evoked responses. To obtain a fuller understanding of how top-down input modulates correlated activity in extrastriate visual cortex, we investigated the changes in correlated activity produced by a top-down working memory signal both in isolation and in combination with bottom-up visual input. We simultaneously recorded the responses of multiple neurons in the middle temporal (MT) area of two macaque monkeys using 16-channel linear array electrodes during the memory guided saccade (MGS) task. In this task the animal had to remember the location of a target and maintain fixation throughout a variable (1-2.5 sec) delay period, then saccade to that location at the end of the trial. In each trial the target was presented either in the same or opposite hemifield relative to the recorded neuron's RF. In almost half of the recording sessions we presented brief (200 ms) visual probes during the memory period, while in other sessions no visual probe was presented. The spatial sensitivity of the neurons was also quantified by measuring their response to probes presented in a 7x7 grid centered around their estimated receptive field (RF) while the animal was fixating. The presence or absence of a visual signal proved crucial for determining the effect of the top-down signal on correlated activity. An isolated top-down spatial signal increases correlations between neurons with similar RFs, but in the presence of a visual probes the top-down spatial signal causes decorrelation, consistent with the results of attention studies. We also found that the top-down spatial signal in isolation decreases the correlated variability of neurons with dissimilar RFs, but in the presence of a visual stimulus this top-down signal increases the noise correlation between dissimilar neurons. We present a descriptive network model to explain how the top-down and bottom-up signals interact to generate the observed patterns of correlated variability among extrastriate cortical neurons.

Disclosures: Y. Merrikhi: None. **B. Noudoost:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

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Program#/Poster#: 149.08/HH23

Topic: D.07. Vision

Support: NSF STC CCF-1231216

Title: Task dependent visual modulations in human intracranial recordings

Authors: *L. ISIK[1], W. LOTTER[2], N. E. CRONE[4], D. D. COX[3], N. G. KANWISHER[5], W. S. ANDERSON[6], G. KREIMAN[7]
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Cambridge, MA; [4]Neurol., Johns Hopkins Hosp., Baltimore, MD; [5]Brain and Cog Sci., 46-4133 MIT, Cambridge, MA; [6]Johns Hopkins, Baltimore, MD; [7]Harvard Med. Sch., Boston, MA

Abstract: We can effortlessly answer many questions about the same visual stimulus. Standard models of visual recognition describe the sequence of processing steps that occur along the ventral visual stream during the first 150 ms after stimulus onset. When and where in the brain does processing start to depend on task? Here we examined the effect of task on visual processing by recording intracranial electrocorticography (ECoG) data from 1176 electrodes, approximately 8% of which were responsive to our visual stimuli, in ten epilepsy patients. Subjects were presented with synthetically generated face stimuli and were cued before each trial to perform one of two possible two-alternative categorization tasks: age (old/young) or gender (male/female). The high gamma power in several visually-responsive electrodes differed between age and gender tasks, despite identical images being present in both tasks. A subset of these electrodes showed task modulations early on, essentially concomitant with the onset of the visual responses, while other electrodes showed late task modulation, after the initial visual evoked response. Intriguingly, we also observed a subset of these electrodes that showed sustained task modulation *before* image onset during the "Fixation" period. These observations show that task modulates visual responses before, during, and after the initial visual response to the stimulus. This progression from pre-stimulus cuing to post-stimulus task representations provides an initial map of the sequence of operations used to transform identical visual inputs into different types of task related information.

Disclosures: L. Isik: None. **W. Lotter:** None. **N.E. Crone:** None. **D.D. Cox:** None. **N.G. Kanwisher:** None. **W.S. Anderson:** None. **G. Kreiman:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 149.09/HH24

Topic: D.07. Vision

Support: DFG SFB 779 TPA1

Title: Mapping feature-based attention in color space in the human

Authors: *M. V. BARTSCH[1], H. STRUMPF[2], S. E. DONOHUE[2,1], H. G. GARCIA-LAZARO[2], M. A. SCHOENFELD[1,2,3], J.-M. HOPF[1,2]
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Abstract: The representation of perceptual color space is supposed to arise in higher- and mid-level ventral extrastriate visual cortex areas. Recently, Stoughton and Conway (2008) examined the population distribution of color-selective cells in posterior inferior temporal cortex of the macaque monkey. They found that the profile contained three prominent peaks (red, green and blue) potentially reflecting the neural basis for unique hues. Here, we (1) ask whether such population response profile would also be obtained in human visual cortex, and (2) investigate the influence of color attention on this profile. We used event-related potentials (ERPs) as a measure of the neural population response, and determined the hue-specific response in the absence of attention to color (analogous to Stoughton and Conway, 2008). To this end, subjects performed a shape discrimination task at fixation, while we recorded the ERP response elicited by monochrome peripheral rings of 45 different colors spanning the whole color space. In a second experiment, we added a central color target at fixation, enabling us to investigate the change of the population response profile when attention was directed towards a specific hue. We found that -in the absence of attention to color- 1) the neural population responses in human visual cortex resembled the profile found in monkeys with the most prominent peak appearing for red, followed by green and blue. The profile evolved at 170ms after onset of the colored rings. 2) Directing attention towards a specific hue led not only to an enhancement of the target hue, but also to a response enhancement of other unattended hues. Finally, attention to different hues was characterized by varying change profiles (modulation size, tuning-width) of the population response.

Disclosures: M.V. Bartsch: None. **H. Strumpf:** None. **S.E. Donohue:** None. **H.G. Garcia-Lazaro:** None. **M.A. Schoenfeld:** None. **J. Hopf:** None.

Poster

149. Spatial and Feature-Based Attention

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Topic: D.07. Vision

Support: NIH R01-EY025648 (JG)

Alfred P. Sloan (JG)

Title: Neural reconstructions of multi-feature objects

Authors: *E. W. DOWD, J. D. GOLOMB
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Abstract: Visual attention allows us to selectively process and enhance a subset of our visual environment. In the real world, multiple objects are often simultaneously present in the

environment, and visual objects typically comprise multiple features (e.g., color and orientation). Thus, attention is rarely static, instead dynamically shifting and splitting across multiple inputs and locations. How can we measure the updating and integration of visual information across dynamic changes of attention? One promising technique is to reconstruct representations of information from activation patterns across entire brain regions, by applying inverted encoding models to fMRI data (Sprague & Serences, 2015). Previous studies have reconstructed representations of visual features (e.g., colors, orientations) and locations from neural activity in visual cortex; these stimulus-specific reconstructions are sensitive to spatial attention (Sprague & Serences, 2013) and feature-based attention (Ester et al., 2016). However, the impact of spatial and feature-based attention on neural reconstructions of *multi-feature* objects is unclear. Here, we present arrays of multi-feature objects at multiple locations, to test whether inverted encoding models can be used to reconstruct task-relevant and irrelevant features that are both spatially attended and unattended. On each trial, two or three colored gratings were presented simultaneously for 1s. Participants were spatially cued to attend to one of the gratings, and were asked to report the task-relevant feature (i.e., color or orientation) using a continuous report task. Behavioral response distributions for the task-relevant feature were fit with probabilistic mixture models. fMRI data were fit with inverted encoding models to reconstruct population-level, feature-selective tuning curves in visual cortex during array presentation. For both color and orientation tasks, the task-relevant feature of the cued (spatially attended) stimulus was successfully reconstructed in V4v and V1, respectively. Task-relevant features of an uncued (spatially unattended) stimulus could also be reconstructed, but with lesser amplitude. We next tested whether task-irrelevant features (e.g., color in an orientation task, or vice versa) could be reconstructed in these same cortical areas. Preliminary results show that task-irrelevant feature information could be reconstructed for spatially attended stimuli but not for spatially unattended stimuli, though reconstructions were significantly worse than for task-relevant features.

Disclosures: **E.W. Dowd:** None. **J.D. Golomb:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

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Topic: D.07. Vision

Support: CAS Grant XDB02050001

CAS Grant Y6CBR41001

Title: Attending multiple locations: The nature of attentional oscillation

Authors: *J. ZHANG[1], Y. JIANG[1], S. HE[1,2]
[1]Inst. of Biophysics, Chinese Acad. of Sci., Beijing, China; [2]Dept. of Psychology, Univ. of Minnesota, Minneapolis, MN

Abstract: Recent behavioral studies revealed that when multiple locations are attended simultaneously, there is an oscillatory effect of attention in the theta-band. However, the cognitive mechanism of such attentional oscillation has not been fully understood. It is unclear whether the observed oscillation reflects the intrinsic cyclic fluctuation of attention, or whether it is caused by the spatial attention switching among multiple locations with relatively fixed amount of time at each location. The former (intrinsic fluctuation) idea predicts that the oscillation frequency is independent of number of locations attended while the latter (sequential visiting) idea predicts the oscillation frequency would decrease with increasing number of attended locations. Here we used behavioral measurement to investigate the temporal dynamics of spatial attention in human observers. In each trial, observers needed to attend three or four locations. After cuing one location, a target was presented at the cued or one of the other attended locations. We tracked the attention dynamics at each location by varying the interval between cue and target onset and recording the detection accuracy at each interval. For the cued location, a gamma-band oscillation was observed in behavioral performance; while for uncued locations, the oscillation was found in the theta-band. We also observed a phase shift in the theta-band oscillation between different uncued locations, suggesting that spatial attention switched among multiple locations. Interestingly, when the number of attended locations increased from three to four, the frequency of attentional oscillation at uncued locations decreased correspondingly. Our results show that the frequency of attentional oscillation in theta-band is not fixed, but rather flexible and task dependent. The rhythm of attention could be modulated by the number of items attended.

Disclosures: **J. Zhang:** None. **Y. Jiang:** None. **S. He:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

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Topic: D.07. Vision

Support: PNI Innovation Fund

Title: Adaptation of spatial attention

Authors: *A. I. WILSON, T. WEBB, M. S. A. GRAZIANO
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Abstract: We recently suggested that attention may be controlled with the help of an internal model of attentional dynamics, similar to the way that the arm is controlled using an internal model of arm dynamics. To evaluate this hypothesis, we tested whether visual attention shows adaptation effects that would suggest an internal model is being updated, just as the control of the arm can adapt to an external force field. We used a standard attentional task (the Posner task). Subjects fixated centrally and a briefly presented visual cue drew exogenous attention to a location in space. 500 ms after the cue, a target stimulus was presented at the cued location or at other locations. Subjects were required to make a discrimination of the target. The relative reaction time to different target locations was used as a measure of the spatial distribution of attention. In the first experiment, a cue to one side of the fixation point predicted a target on the opposite side of the fixation point (85% predictive). Subjects showed a change in behavior over a series of 300 trials. By 200 trials, attention was automatically directed to the location opposite the cue - even though, when asked afterward, less than 20% of subjects explicitly noticed the relationship between the cue and the target. In a second experiment, a cue at one peripheral location predicted a target displaced 45 degrees clockwise in a circle around the fixation point (85% predictive). Again, subjects showed an adaptation of attention such that the cue caused an automatic redirection of attention to the clockwise-displaced location. In that experiment, only 2% of subjects explicitly noticed the relationship between the cue and the target. These findings suggest that exogenous visual attention is not just a reflexive, hard-wired process, but is adaptable over repeated trials in which the cue that initially draws attention is displaced from the eventual visual target. Moreover, the adaptation occurs at an implicit level, without requiring any explicit knowledge of the contingencies. This evidence is consistent with the proposal that attentional control, like control of the arm, includes an adaptable internal model of the dynamics of the item being controlled.

Disclosures: A.I. Wilson: None. **T. Webb:** None. **M.S.A. Graziano:** None.

Poster

149. Spatial and Feature-Based Attention

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 149.13/HH28

Topic: D.07. Vision

Title: Allocation of spatial attention reduces trial-by-trial neural variability in humans

Authors: *A. ARAZI[1], Y. YESHURUN[3], I. DINSTEIN[2]
[1]Dept. of brain and cognitive science, [2]Dept. of Psychology, Ben Gurion Univ., Beer Sheva, Israel; [3]Dept. of Psychology, Univ. of Haifa, Hifa, Israel

Abstract: Introduction: Previous electrophysiology studies in animals have reported that attention improves behavioral performance primarily by reducing neural variability across trials.

Here, we examined the relationship between neural variability and spatial visual attention in human subjects as they performed an orientation discrimination task that was preceded by a spatial cue while their neural responses were recorded with EEG.**Methods:** Twenty-five subjects participated in the study. Their attention was manipulated by an arrow, which preceded the target stimulus and either accurately predicted the target location (valid trials), diverted their attention away from the target location (invalid trials), or was not informative (neutral trials - double headed arrow). The target stimulus was presented on either right or left of fixation and consisted of a Gabor that was tilted to the left or right of vertical. In 60% of the trials the cue was valid, in 20% of the trials the cue was invalid, and in 20% of the trials the cue was neutral. Neural responses were recorded with EEG. We quantified mean ERP response, trial-by-trial variance, and Inter-trial-phase-coherence (ITPC) of the cue evoked activity in each subject.**Results:** Our results reveled that N170 responses were lateralized according to the cue, with significantly larger negative amplitudes in the contralateral electrodes to the visual field that was cued. Furthermore, ITPC in the Theta (4-8Hz) and Alpha (8-13Hz) frequency bands was larger in the contralateral electrodes relative to the cued visual field, 100-400ms following cue presentation. Most importantly, individual magnitudes of ITPC were associated with better accuracy and better perceptual performance in the orientation discrimination task. **Conclusions:** Allocating attention to a specific spatial location is associated with larger phase coherence across trials, suggesting that attention reduces the variability in the timing\latency of the responses and improves perceptual performance.

Disclosures: A. Arazi: None. **Y. Yeshurun:** None. **I. Dinstein:** None.

Poster

149. Spatial and Feature-Based Attention

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Topic: D.07. Vision

Support: EY025018

Title: High-attention demand training induces plasticity of the visual system in adults with amblyopia

Authors: *I. J. ÜNER, X. LAI, C. HOU
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Abstract: Amblyopia is the most common cause of visual acuity loss in early childhood and affects about 3% of the population. In addition to the acuity loss, a high proportion of amblyopic patients lack binocular function and depth perception. The standard clinical treatment is to patch the non-amblyopic fellow eye to promote the use of the amblyopic eye in children. It has long

been argued that adult amblyopia is an untreatable condition because it has passed the sensitive period of development. However, a number of studies suggest that repetitive practice (perceptual learning) of a visual task using the amblyopic eye improves visual performance in both children and adults with amblyopia. It has also been reported that there are deficits in the amblyopic eye for tasks that demand spatial attention (Sharma et al., 2000; Popple & Levi, 2008; Secen et al., 2011; Hou et al., 2016). In this study, we hypothesize that training adult amblyopes with high-attention demand tasks improves their visual functions. We designed a dichoptic "feature counting" perceptual learning paradigm, which requires rapid shifts in attention and is a high-attention demand task (Egeth et al., 2008; Anobile et al., 2012). The stimuli consist of a randomly positioned array of highly-visible low spatial frequency Gabors, so that the targets are easily visible to both the amblyopic and fellow eye. We set the vertical Gabors onto the tested eye and the horizontal Gabors onto the non-tested eye, viewing through mirror stereoscope. The task is to search for and count the vertical Gabors in the cued eye and to ignore the horizontal Gabors in the un-cued eye. We arranged 90% of the trials with vertical Gabors to the amblyopic eye and only 10% of the trials with vertical Gabors to the fellow eye. The training was about two visits per week and two hours per visit for two months. Our results show that training with feature counting tasks in adult amblyopes results in a substantial improvement not only in spatial attention (feature counting performance), but also in fundamental visual functions including visual acuity, position acuity, contrast sensitivity and stereoacuity. Our results demonstrate that high-attention demand training induces plasticity of the visual system in adults with amblyopia. Taken as a pilot study, this work suggests that training with high-attention demand tasks may provide important insight for treating amblyopia and perhaps other cortical dysfunctions.

Disclosures: I.J. Üner: None. **X. Lai:** None. **C. Hou:** None.

Poster

149. Spatial and Feature-Based Attention

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 149.15/HH30

Topic: D.07. Vision

Support: I01CX000744

Title: Attentional biases in vertical space with age

Authors: *D. G. LAMB[1], J. B. WILLIAMSON[1], A. R. WALKER[2], S. DATTA[2], K. M. HEILMAN[1]
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Abstract: When interacting with the environment the preponderance of information is well beyond one's capacity to fully process; attention is the triage process that allocates these

resources. One means of triaging is directing attention to portions of egocentric space. Vertical attentional biases may be important in avoiding falls, a key risk factor in morbidity amongst aging populations. To learn if there are vertical spatial attentional biases and how these change with age, we evaluated the allocation of vertical spatial attention as a function of the space by using solid and character vertical line bisections and trisections presented in left, right and mid-sagittal space and, above, below or at eye level on a large format touchscreen monitor. We found significant effects of age ($p<0.01$), and spatial location ($p<0.01$), as well as an interaction between age and spatial condition ($p<0.01$), with an upwards bias in younger participants. On an attentional scan variant of the solid bisection task, we found significant effects of age ($p<0.01$) and probe presentation direction ($p<0.01$), but neither horizontal or vertical spatial location, as well as an interaction between the vertical spatial location and probe presentation direction ($p<0.01$). Interestingly, the upward bias in younger participants relative to older participants was reversed in this task.

Disclosures: D.G. Lamb: None. **J.B. Williamson:** None. **A.R. Walker:** None. **S. Datta:** None. **K.M. Heilman:** None.

Poster

149. Spatial and Feature-Based Attention

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Program#/Poster#: 149.16/HH31

Topic: D.07. Vision

Support: ICM P09-015-F

Title: Sensory motor demand and immersion in video gamers' attentional skills

Authors: *P. E. MALDONADO[1], C. MOENNE[2], R. C. VERGARA[3], E. LORCA[3], C. LARRAGUIBEL[3], G. LAM[3], A. HERNÁNDEZ-CORVALÁN[3]
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Abstract: During the past 15 years, a great amount of work has shown that playing video games can improve visual attention. It has been even proposed as a possible therapy for people who had minor visual impairments. However, the mechanisms explaining why this improvement takes place is still unknown. Here we proposed that video games demand the optimization of at least one of two attentional mechanisms; maintaining attention while being strongly resistant to distractors (immersion), and fine tuning between attentional and motor systems (sensory-motor demand). To test this hypothesis, we developed a video game questionnaire that includes questions depicting regarding the strength of the immersion experience and the sensory motor demand training in the general population of video game players. Using more than a hundred

people we validated the questionnaire using Factor Analysis and Cronbach's Alpha. We then invited subject to an in-lab procedure where they answered the validated questionnaire and performed an attentional flanker task. We then used the scores of the validated video game questionnaire scales (immersion and sensory-motor demand) to predict task performance, and the amplitude of EEG evoked potential commonly analyzed for each of these tasks. Results reported here supports that early attentional P1 component is predicted by immersion score, while late frontal P3 was predicted by sensory-motor demand. Only sensory motor demand predicted behavioral results, suggesting longer reaction times for players with higher sensory demand scores. Our results support that the immersion and sensory motor demand needed during usual game play do modify classic attentional components, suggesting them as key mechanisms in this improvement. These findings represent the first step in understanding the neural mechanism which explains the attentional improvement produced by video games, giving hints of how an ad hoc game for therapy should be built.

Disclosures: P.E. Maldonado: None. **C. Moenne:** None. **R.C. Vergara:** None. **E. Lorca:** None. **C. Larraguibel:** None. **G. Lam:** None. **A. Hernández-Corvalán:** None.

Poster

149. Spatial and Feature-Based Attention

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 149.17/HH32

Topic: D.07. Vision

Title: Attenuation of visual search deficits in low luminance environments through complimentary tactile stimulation

Authors: M. HUNTER[1], B. OLK[2], *B. GODDE[1]
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Abstract: Little is known about visual search processes and subsequently about contributing factors and mechanisms underlying performance decreases in low luminance conditions (<0.5 cd/m2) [1]. We provided contrast efficiency functions for simple visual search tasks within this spectrum, relating the cumulative effect of relative contrast luminance and the innate contrast of target stimuli to search performance [2]. Additionally, different aspects of tactile stimulation (predictive probability of a tactile stimulus, or type of encoding) could attenuate performance decreases and its fitting along the efficiency function. We presented the idea of a "gating window" for the adoption of tactile stimuli to be effective as a function of decreasing luminance contrast; however, the neurophysiological mechanisms of these functions have yet to be incorporated elucidating the primary factor for decreases in performance.
We obtained event related potentials (ERP) from eleven participants while they performed a

tactile-visual search task incorporating three different types of tactile encoding, i.e. frequency (20 Hz and 40 Hz stimulation), spatial (left vs right), and frequency and spatial, to provide information about the location of the target. We confirmed that tactile stimuli can attenuate decreases in performance under low luminance conditions; however, this was not specific to encoding type. The ERP results primarily implicated the N2 component as contributing factor with correlations for RT (0.87; $p < 0.01$) and for d' (-0.83; $p < 0.01$); increased peak latencies reflect slower RTs and decreased performance. These correlations remained consistent independent of coding.
Results provide preliminary evidence and verification of the distinct integration gating component reported previously. While this is significant with respect to the understanding of the search process with respect to our paradigms further testing needs to be done for generalization to other search paradigms.
[1] Zele AJ, Cao D. Vision under mesopic and scotopic illumination. Front Psychol. 2015 Jan 22; 5:1594 [2] Hunter M, Godde B, Olk, B (2017) Effects of Absolute Luminance and Luminance Contrast on Visual Discrimination Task in Low Mesopic Stimuli. Attention, Perception, & Psychophysics, 79(1), 243-252.

Disclosures: M. Hunter: None. **B. Olk:** None. **B. Godde:** None.

Poster

150. Eye Movements

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Topic: E.01. Eye Movements

Support: Deutsche Forschungsgemeinschaft (FOR 1847-A3 TH425/13-1)

Title: Blink associated eye movements (BARMs) complement microsaccades in correcting for fixation errors

Authors: *M. F. KHAZALI, J. POMPER, P. THIER
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Abstract: Blinks do not only protect the eye and keep it hydrated, but they do also correct for eye position deviations by blink-associated resetting eye movements (BARMs) as demonstrated in humans (Khazali et al. Elife. 2016. 5). To bond blinks and resetting eye movements in a synergy has the ecological advantage to keep the overall downtime of vision minimal as both, blinks and eye movements will compromise clear vision (Bristow et al. Curr Biol. 2005. 15). Although BARMs are functionally distinct from other eye movements in the torsional dimension (Khazali et al. Elife. 2016. 5), it has remained open if BARMs observed in the horizontal and vertical dimensions (fixational BARMs) are not in fact microsaccades coinciding with blinks. To

clarify this question we made use of a huge number of blinks recorded with permanently implanted search eye coils in non-human primates, allowing a rigorous characterization of fixational BARMs. We show here that these fixational BARMs are indeed distinct from microsaccades and that they serve a complementary role to microsaccades in resetting eye position. First of all, they compensate for large fixational errors more efficiently than microsaccades, secondly, their probability to be executed in eccentric eye positions is higher, and thirdly, they reset the eyes into a zone around the target location that is broader than the one for a microsaccades. Taken together, these findings suggest that fixational BARMs help to keep the eyes in a working range wherein microsaccades guarantee high acuity vision. Moreover, we show that these fixational BARMs operate in a retina-centric frame of reference, i.e. they reset the line of sight to the target location independent of where the target is located with respect to the head.

Disclosures: **M.F. Khazali:** None. **J. Pomper:** None. **P. Thier:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.02/HH34

Topic: E.01. Eye Movements

Support: Blind Children Center

Knights Templar Eye Foundation

Title: Fixation in strabismus patients before and after surgery

Authors: *F. F. GHASIA[1], C. GALLAGHER[2], J. OTERO-MILLAN[3], A. G. SHAIKH[4]
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Abstract: Introduction: Microsaccades are miniature eye movements that constantly change the gaze during attempted visual fixation. Saccades and microsaccades represent an oculomotor continuum and are produced by common neural machinery. Strabismic patients have impaired binocular horizontal saccades as well as fixational eye movements. We examined the fixational eye movements in strabismic patients with and without latent nystagmus (LN) before and after surgery. **Methods:** Eye movements were recorded with infrared video-oculography in 13 strabismic patients (preop stereopsis present=3; stereopsis absent=10) with LN (n =8) and without LN (n=5) and 13 controls while they performed a visual fixation task. 6 out of the 13 patients (LN =3 no LN=3) had improvement in stereopsis post surgery. **Results:** Strabismic patients with and without LN had greater fixation scatter in both the viewing (bivariate contour

ellipse area (BCEA) normals: -0.49; strab with LN: 0.06, strabismus without LN: -0.2800, $p<0.05$ one way ANOVA) and non-viewing eye (BCEA: normals: -0.48; strab with LN: 0.55, strabismus without LN: -0.04, $p<0.05$ one way ANOVA) before surgery. The fixational saccades in strabismic patients without LN were disconjugate. The disconjugacy of fixational saccade between the viewing and non-viewing eye decreased after strabismus repair (disconjugacy preop: 0.19 ± 0.33; disconjugacy postop 0.15 ± 0.23, $p=0.01$ unpaired t test). A similar decrease in the disconjugacy of amplitude of quick phases of LN was noted before and after surgery (disconjugacy preop: 0.43 ± 0.70; disconjugacy postop 0.26 ± 0.58, $p<0.001$ unpaired t test)
Discussion: Microsaccades and quick phases of LN are disconjugate in strabismic patients and exceed the capabilities of the sensory system to achieve fusion. The disconjugacy is reduced after surgical repair thereby facilitating fusion in patients with and without latent nystagmus.

Disclosures: F.F. Ghasia: None. **C. Gallagher:** None. **J. Otero-Millan:** None. **A.G. Shaikh:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.03/HH35

Topic: E.01. Eye Movements

Support: R01 EY022854

R01 EY02831

T32 DC011499

Title: Ventral premotor cortex activity during head and eye movements

Authors: *I. SMALIANCHUK[1], N. J. GANDHI[2]
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Abstract: The ability to coordinate movements across multiple effectors is essential for survival and success. Within the oculomotor system, a robust mechanism exists to produce orienting behavior with a combined movement of the eyes and the head. However, flexibility must be ensured to change the coordination properties according to context. The context-based heterogeneity of behavior can be explained through cortical control of movements. We suggest that the ventral premotor cortex (PMv) influences the context-based properties of head-unrestrained gaze shifts. The PMv is known for differentiating between contexts of the task (Festante et al. 2016; Fluet et al. 2010). Furthermore, there are projections from the PMv to the muscles of the neck and the eye (Billig & Strick 2012), thus making this area of the cortex an ideal candidate. In this study, we systematically explored the role of PMv in gaze shifts. We

recorded single units from PMv while the animal was performing various head and eye movement tasks. These included head-unrestrained paradigms in which the animal moved the eyes independent of the head, the head independent of the eyes, and combined eye-head movements. The head position was recorded in three axes of rotation to account for the tilt which occurs during rotation. We found that neurons in a specific area of PMv increase activity as a precursor to a gaze-shift. Some of the cells were selective to the context under which the eye movement was performed, primarily differentiating between different relative head and eye positions during the gaze shift. This preliminary evidence suggests direct PMv involvement in eye-head coordination during head-unrestrained gaze shifts.

Disclosures: I. Smalianchuk: None. **N.J. Gandhi:** None.

Poster

150. Eye Movements

Location: Halls A-C

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Topic: E.01. Eye Movements

Support: Brain/MINDS from MEXT and AMED

MEXT KAKENHI Grant Number 15H01673

the Brain Sciences Project of CNSI, NINS (Grant Number BS271004)

Title: Head-unrestrained eye-tracking in macaque monkeys

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Abstract: [Introduction] Conventional methods for eye tracking in non-human primates require invasive techniques such as implantation of a head holder and/or a scleral search coil. Such invasive procedures are potential barriers for high throughput screening of eye movement behavior during free-viewing in non-human primates. One possible solution for this problem is to use a ‘remote-type’ eye tracker, which uses CCD cameras to detect eye positions in the world coordinate and thus allows head motion in a certain range. Successful recording of eye movements using a remote-type eye tracker for chimpanzees under a head-unrestrained condition (Kano and Tomonaga 2009) has already been reported. Here we examined whether eye movements of macaque monkeys can be measured using a remote-type eye tracker under a head-

unrestrained condition. [Methods] As a remote-type eye tracker, Tobii TX300 (300Hz in temporal resolution and 0.4 degree in spatial accuracy) was used in this study. In three macaque monkeys that were trained to sit on a monkey chair, natural or complex images were presented as test images on a 21-inch LCD display. All 56 test images were identical to those used for studies of eye movements during free-viewing in subjects with schizophrenia (Miura et. al. 2014 and Morita et. al. 2016). The test images were presented for 8 seconds in a random order, interleaved with a 4-sec presentation of a calibration image in which small pictures of a monkey face are embedded in four corners of the gray background. [Results] In all three monkeys, the eye positions during the presentation of the calibration image were naturally drawn to either of four corners, which enabled calibration of eye positions. The percentage of time with successful recording of bilateral eye positions among total time for image presentation was calculated. In monkey A, for example, trials with >50% successful recording was obtained from all of 7 sessions. In all three monkeys, saccades were reliably detected so that we can plot the peak velocity of the saccades across the amplitude of the saccades (the main-sequence). The slope of the main sequence, the amplitude of saccades and the frequency of saccades were comparable to those of eye movement data obtained from three other Japanese monkeys viewing the same test images using a scleral search coil method under a head-restrained condition. [Summary] These results suggest that head-unrestrained eye tracking in macaque monkeys during free-viewing is a promising method for evaluating eye movements in primate models for attentional disorders such as schizophrenia or unilateral spatial neglect.

Disclosures: **M. Yoshida:** None. **K. Tsujimoto:** None. **K. Miura:** None. **A. Takemura:** None. **M. Iwase:** None. **R. Hashimoto:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.05/II1

Topic: E.01. Eye Movements

Support: EY014263

Title: Two midbrain premotor populations controlling lens accommodation in the primate

Authors: ***P. J. MAY**[1], I. BILLIG[2], J. J. QUINET[3], P. D. GAMLIN[4]
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Abstract: Each target we look at lies at a discrete distance from the viewer. To focus on near targets, we increase lens curvature through the actions of the ciliary muscle. This lens accommodation, along with converging the eyes and constricting the pupil, makes up the near response. The final common path for lens accommodation is a two cell circuit: preganglionic motoneurons in the Edinger-Westphal nucleus (EWpg) project upon postganglionic motoneurons in the ciliary ganglion that in turn supply the ciliary muscle. To date, we have little understanding of central circuits that control lens accommodation, in general, and that supply EWpg, in particular. Physiological studies point to a set of premotor cells, termed the midbrain near response neurons, that are believed to lie in either the supraoculomotor area (SOA), or in the adjacent midbrain reticular formation (MRF). There is also anatomical evidence for a projection by the central portion of the MRF (cMRF) onto the EWpg. These cMRF neurons may or may not include the midbrain near response cells. In this study, we identified the premotor populations controlling lens accommodation by using the n2c strain of rabies virus as a retrograde trans-synaptic tracer and injecting it into the ciliary muscle of macaque monkeys (n=5)*. The locations of infected neurons were determined using immunohistochemistry**. Premotor neurons were immunochemically discriminated from preganglionic motoneurons. Two separate populations of premotor neurons were identified. The first was primarily located within the SOA. This population was densest caudally, where it formed a bilateral band over the oculomotor nucleus that extended laterally into the immediately adjacent MRF. These premotor cells likely represent midbrain near response neurons. Associated with this population was a smaller number of cells that extended along the midline between the oculomotor nuclei and clung to the edge of the medial longitudinal fasciculus. A second population of labeled cells was located more laterally, in the cMRF. These neurons formed a band located in the region known to receive collicular terminals. They may represent the cMRF population that is believed to be active during disjunctive saccades. These saccades move the eyes between targets that lie at different distances from the observer. These two midbrain populations of premotor neurons appear to be anatomically discrete, suggesting that they differ functionally.
*All surgeries took place at the University of Pittsburgh in the Center for Neuroanatomy and Neurotropic Viruses directed by Peter L. Strick, PhD
** This procedure was made possible by a donation of anti-rabies virus by Matthias Schnell, PhD.

Disclosures: **P.J. May:** None. **I. Billig:** None. **J.J. Quinet:** None. **P.D. Gamlin:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.06/II2

Topic: E.01. Eye Movements

Support: NEI Grant EY014263

Title: Are there distinct roles for SOA and cMRF premotor neurons in disconjugate eye movements in the primate?

Authors: *J. J. QUINET[1], K. SCHULTZ[1], P. J. MAY[2], P. D. GAMLIN[1]
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Abstract: To look at targets located in 3D space, we often make disconjugate eye movements where the eyes move unequal amounts in the same direction, or in opposite directions for midline targets. The neural strategy used to execute these types of eye movements is still debated, with two opposing models being considered. The Hering model suggests that there are separate conjugate and vergence controllers with each eye receiving neural commands from each controller to produce the appropriate eye movement, whereas the Helmhotz model suggests that each eye is controlled independently. A report from Waitzman et al (2008) suggested that central mesencephalic reticular formation (cMRF) neurons had eye-specific activity and that their stimulation produced disjunctive saccades. A recent anatomical study (Bohlen et al 2016) revealed that the cMRF projects to the preganglionic Edinger-Westphal nucleus and medial rectus motoneurons, suggesting a role in the near response.
In the present study, we examined the role of premotor cells in the SOA and cMRF during disconjugate eye movements. We recorded both saccade and vergence-related cells in two monkeys as the animals oriented their gaze towards targets at various 3D locations. We also tested conjugate and pursuit eye movement sensitivity.
We found that the populations of eye movement sensitive neurons in the two recording locations displayed different characteristics. In the SOA, near the oculomotor nucleus, cells defined as near- or far-response exhibited increased, predominantly tonic, firing rates for only convergent or divergent eye movements, respectively. In the cMRF, the most common cell type displayed activity that correlated with both position and speed of symmetrical convergent or divergent eye movements. These cells also displayed a burst of activity during disjunctive vergence eye movements, but not during saccadic eye movements. In addition, we encountered a class of neuron that showed a burst of activity associated solely with the dynamic component of saccade-vergence eye movements, but which displayed no apparent change in activity for either symmetric vergence eye movements or for conjugate saccades. To our knowledge, this is the first report of this class of vergence-related neuron, but the existence of such saccade-vergence burst neurons was suggested previously (Kumar et al., 2006).
These results suggest that the different populations of premotor neurons found in the SOA and cMRF contribute differentially to the generation and dynamics of disconjugate eye movements. In addition, these SOA and cMRF premotor neurons could contribute to a common vergence integrator.

Disclosures: J.J. Quinet: None. **K. Schultz:** None. **P.J. May:** None. **P.D. Gamlin:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.07/II3

Topic: E.01. Eye Movements

Support: NEI EY008313

Research to Prevent Blindness

Title: Absence of compensatory hypertrophy of rectus extraocular muscles in monkey superior oblique palsy

Authors: *A. LE[1], A. FERGUSON[1], V. POUKENS[1], H. S. YING[3], D. S. ZEE[4], J. L. DEMER[2]
[1]Ophthalmology, [2]Jules Stein Eye Inst., UCLA, Los Angeles, CA; [3]Boston Univ., Boston, MA; [4]Dept Neurol, Johns Hopkins Hosp. and Hlth. Syst., Baltimore, MD

Abstract: Magnetic resonance imaging (MRI) in humans with unilateral superior oblique (SO) palsy indicates presumably compensatory hypertrophy of some rectus extraocular muscles (EOMs), including the ipsilesional lateral rectus (LR) and inferior rectus (IR), and contralesional superior rectus (SR). We investigate whether compensatory rectus EOM size change occurs in monkeys with unilateral SO palsy produced by experimental subarachnoid trochlear neurectomy. Whole orbits from rhesus macaque monkeys were formalin fixed, embedded whole in paraffin, sectioned coronally at 10 μm thickness, and stained with Masson's trichrome. Muscle volumes were estimated using shrinkage-corrected cross-sectional areas of the EOMs measured every 100 μm through the entirety of each muscle. Muscle fibers were identified by color thresholds. Values in each specimen were normalized to average total EOM volume in normal monkeys. Eleven normal monkey orbits analyzed used to determine normative volumes for each EOM that were compared to EOM volumes from the ipsilesional and contralesional orbits with SO palsy. The ispilesional SO had a significant volume reduction of 26±5% ($P<0.0001$). In 4 specimens with SO palsy, ipsilesional and contralesional rectus EOM volumes were statistically similar to normative values ($P>0.94$).
In contrast to MRI findings in human unilateral SO palsy, unilateral trochlear neurectomy in monkey produces no significant compensatory changes in post-mortem rectus EOM volumes. This could represent a species difference, or reflect a functional EOM volume change related to contractile state only evident in vivo.

Disclosures: A. Le: None. **A. Ferguson:** None. **V. Poukens:** None. **H.S. Ying:** None. **D.S. Zee:** None. **J.L. Demer:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.08/II4

Topic: E.01. Eye Movements

Support: NIH NEI EY008313

Research to Prevent Blindness

Title: Inferior compartment of medial rectus muscle fails to relax during near fusional divergence

Authors: *J. L. DEMER[1], R. A. CLARK[2]
[1]Jules Stein Eye Inst., [2]Stein Eye Inst., UCLA, Los Angeles, CA

Abstract: Fusional binocular divergence is required when changing binocular fixation from near to far objects, but it is also required to maintain fusion in the face of pathological mechanical or neural biases towards convergence. The superior compartment of the medial rectus muscle (MRs) has been shown (Demer & Clark, *J. Neurophysiol*. 112: 845, 2013) by magnetic resonance imaging (MRI) to have greater contractility in both convergence and conjugate adduction than the inferior medial rectus compartment (MRi). We asked if MRs might also play a specialized role in fusional divergence.

In 10 adults, surface coil MRI was repeated in axial, coronal, and sagittal planes for each orbit during binocular fusion of a centered, near accommodative target at 20 cm, and repeated during monocular viewing of the same target by each eye through 8PD base in prism inducing divergence. Contractility, indicated by change in posterior partial volume (PPV), was analyzed by automated algorithm in the transverse halves of each rectus muscle, and in the medial (equatorial insertion, torsion) and lateral (posterior insertion, vertical) superior oblique (SO) compartments. Contractility of the inferior oblique (IO) muscle was evaluated by change in its cross section at the center of the inferior rectus muscle. MRI confirmed expected 2.5±0.6° (SEM) divergence of prism viewing eyes without significant vertical movements.

Abduction of the diverging eye was associated with 4.2±1.5% whole lateral rectus (LR) PPV increase ($P<0.05$), with no asymmetry between inferior and superior LR compartments. During abduction of the diverging eye, there was 1.7±1.1% overall decrease in PPV of the MR; however, this was entirely attributable to 3.1% reduction in MRs PPV ($P<0.025$), with no significant change (0.4±1.0%) in MRi, or in any muscles of the non-prism viewing eye. In the medial compartment SOm of the diverging, prism viewing eye there was 6.1±2.9% PPV reduction, with no significant change in lateral compartment SOl. There was no significant contractile change in the IO cross section of either eye.

These results confirm and extend to divergence the particularly active role of the superior MR

compartment in horizontal vergence. Moreover, the failure of inferior MR compartment to relax during divergence implies co-contraction in the horizontal rectus muscles, a phenomenon consistent with motor neuron recordings in monkey (Miller et al, *J. Neurophysiol*. 105:2863, 2011) yet heretofore undemonstrated by direct force measurement.

Disclosures: J.L. Demer: None. **R.A. Clark:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.09/II5

Topic: E.01. Eye Movements

Support: NEI EY008313

Research to Prevent Blindness

Title: Intramuscular innervation of global and orbital layers of primate lateral rectus (LR) muscle

Authors: *A. BAIG[1], A. LE[1], A. FERGUSON[2], V. POUKENS[2], J. L. DEMER[3]
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Abstract: Horizontal rectus muscles exhibit neuromuscular compartmentalization. The abducens nerve (CN6) bifurcates into superior and inferior divisions innervating corresponding LR regions. Although differential contraction and electrical activity of the orbital (OL) and global (GL) layers has been demonstrated, selective innervation has not. This study investigated possible selective innervation of the OL and GL in human LR.
A 1.4 year old, whole human orbit was exenterated en bloc, formalin fixed, paraffin embedded, sectioned coronally at 10 μm thickness, and stained with Masson's trichrome. Branches of CN6 were traced in serial sections to their terminal arborizations. Nerve profiles and muscle fibers were marked using mask layers in Photoshop, then reconstructed in 3-D using ImageJ.
CN6 bifurcated into superior and inferior divisions prior to entering the LR on its global surface, with the inferior division entering more posteriorly and the superior division more anteriorly. Corresponding CN6 arborizations remained within respective muscle compartments, but fine continuations of each arborization transited the GL into the overlying OL. In the inferior compartment, OL terminations were mainly in the LR mid-belly. The superior CN6 division terminated in the OL more anteriorly than the inferior. In contrast to mid-belly predominance of OL terminations, GL terminations were distributed uniformly throughout the anteroposterior LR. In contrast to the distinct peripheral topography of motor innervation in inferior and superior LR compartments, differential innervation to GL and OL is at a much finer level and occurs deep

within the muscle. Thus, while anatomically selective pathological and experimental denervations can selectively target only the inferior or superior LR, selective neural lesions involving only GL or OL appear anatomically implausible.

Disclosures: **A. Baig:** None. **A. Le:** None. **A. Ferguson:** None. **V. Poukens:** None. **J.L. Demer:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.10/II6

Topic: E.01. Eye Movements

Support: NEI EY008313

Research to Prevent Blindness

Title: Elastin content of primate optic nerve sheath and pia

Authors: ***M. VASUDEV**[1], A. KOKOYAN[1], A. LE[2], V. POUKENS[1], J. L. DEMER[3]
[2]Ophthalmology, [1]Univ. of California Los Angeles, Los Angeles, CA; [3]Jules Stein Eye Inst., UCLA, Los Angeles, CA

Abstract: The human optic nerve (ON) sheath is bilaminar and is mechanically loaded by tension when the optic nerve becomes taut in adduction. In monkey, we investigated the microanatomy of the ON sheath and pia investing the ON sheath to determine if the histological properties are consistent with the biomechanical loading.
Three monkey orbits ages 2.5, 3, and 14 yrs, and 3 human orbits ages 44, 59, and 65 years were formalin fixed, embedded whole in paraffin, and sectioned in the coronal plane at 10 μm thickness. Sections at 100 microns intervals throughout the orbit were stained with van Gieson elastin stain. Microscopy was used to quantify the regional distribution of black elastin fibers. Since sections were thick relative to depth of focus, focal position was used to ascertain relative obliquity of fibers to plane of sectioning. Within coronal sections, fibers orientated circumferentially around the ON appeared as long segments. Fibers running longitudinally along the length of the ON appeared as small segments. Obliquely orientated fibers, confirmed by depth of focus analysis, had intermediate lengths compared to the circumferential and longitudinal fibers.
Elastin fiber length in the ON sheath and pia of monkey and human was unimodally distributed with a peak favoring oblique fibers between 2 and 13 μm ($P<0.0001$) long, and were uniformly distributed throughout the perimeter of the pia and ONS. In human ON pia, there were on average more thin (213±16, ±SEM, n=10 sections) than thick fibers (111±18, $P<0.0001$).

Elastin fiber thickness in human ON pia was bimodally distributed into thin and (averaging 0.49± 0.02 μm) and thick (0.94±0.08 μm) distributions, whereas elastin fiber thickness in monkey was unimodal (averaging 0.73±0.03 μm).
In both monkey and human, the investing pia of the ON, and its enveloping sheath, both contain heavy deposits of elastin fibers having a wide range of orientations that would permit these structures to resist mechanical stress similarly in all directions, and so could form the basis of biomechanically isotropic behavior. This is consistent with the mechanical loading on the ON that occurs during eye movements.

Disclosures: **M. Vasudev:** None. **A. Kokoyan:** None. **A. Le:** None. **V. Poukens:** None. **J.L. Demer:** None.

Poster

150. Eye Movements

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Program#/Poster#: 150.11/II7

Topic: E.01. Eye Movements

Support: ERC starting grant

ATIP-Avenir

Title: Light-sheet based whole-brain neuronal activity recording during vestibular stimulation

Authors: ***V. BORMUTH**, G. DEBRÉGEAS, R. CANDELIER, G. MIGAULT
Lab. Jean Perrin, Univ. Pierre Et Marie Curie, Paris, France

Abstract: Light-sheet microscopy allows cell resolved whole-brain calcium imaging at several brain scans per second in zebrafish larvae. Currently this technique is not compatible with dynamic stimulation of the vestibular system. We developed an ultra stable miniaturized light-sheet microscope that can be rotated while performing whole-brain recordings. Rotating the microscope rotates the fish and stimulates the vestibular system while imaging always the same plane in the brain. We demonstrate volumetric whole-brain neuronal activity recordings during vestibular stimulation. We mapped the brain activity with cellular resolution of the vestibulo-ocular reflex.

Disclosures: **V. Bormuth:** None. **G. Debrégeas:** None. **R. Candelier:** None. **G. Migault:** None.

Poster

150. Eye Movements

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Program#/Poster#: 150.12/II8

Topic: E.01. Eye Movements

Support: EY024848

EY06069

EY026274

ORIP P51OD010425

Research to Prevent Blindness

Title: Investigating the potential neural basis of pattern strabismus in the horizontal and vertical oculomotor neural integrators

Authors: *A. PALLUS[1], M. M. WALTON[2], M. J. MUSTARI[3]
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Abstract: Infantile strabismus is a common disorder that is characterized by multiple visual and oculomotor abnormalities, including chronic horizontal and vertical misalignment of the eyes. Often, this includes a pattern strabismus, in which the misalignment of the eyes varies orthogonally with eye position. Several researchers have proposed that this is due to abnormal cross coupling between normally horizontal and vertical oculomotor subsystems. The development of non-human primate models of infantile strabismus has allowed researchers to investigate the neural mechanisms underlying the symptoms of the disorder. Previous studies from our laboratory have shown abnormal directional tuning in saccadic burst generators. Because cross coupling persists across multiple movement types, we hypothesized that the oculomotor neural integrators may encode abnormal signals strabismus. In this study, we test the hypothesis by recording the activity of individual neurons in the nucleus prepositus hypoglossi (NPH) and the interstitial nucleus of Cajal (INC) in three monkeys (Macaca mulatta), one normal and two with pattern strabismus, during a saccade task. These two structures are considered to be the locations of the horizontal and vertical neural integrators, respectively. In general, we found increased variability in the tonic firing rate compared with normal controls in both structures. The preferred directions of the two populations of cells were still in the appropriate direction, on average, but the distribution of directional preferences was more widely distributed in strabismus. Stimulation of the normal INC has been shown to produce conjugate vertical eye movements, but stimulation of the INC in the same region of our neurophysiological recordings

produced disconjugate eye movements, often with the ipsilateral eye moving horizontally. Importantly, the eyes remained in the new positions after stimulation ended suggesting that this effect was due to activity within the integrator rather than an activation of the nearby oculomotor nucleus. These results are consistent with the hypothesis that the oculomotor neural integrators are involved in the inappropriate cross-coupling that may be responsible for producing pattern strabismus, but further study is required to determine whether this is sufficient to produce the behavior or if the cross-coupling is distributed among multiple structures within the oculomotor system.

Disclosures: A. Pallus: None. **M.M. Walton:** None. **M.J. Mustari:** None.

Poster

150. Eye Movements

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Program#/Poster#: 150.13/II9

Topic: E.01. Eye Movements

Support: Leon Levy Foundation

Fight For Sight

Title: Characteristics of rebound nystagmus in healthy subjects

Authors: *J. OTERO-MILLAN[1], A. COLPAK[2], D. S. ZEE[3], A. KHERADMAND[3]
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Abstract: Accurate and stable gaze holding is achieved by a complex network within the brainstem and cerebellum. Adaptation of network can result in a rebound nystagmus when looking straight ahead after holding the eyes in eccentric positions, with slow phases in the direction of the former eccentric position. Although rebound nystagmus is a clinical sign of cerebellar dysfunction it also occurs with less intensity in healthy individuals, especially if fixation is removed upon the return to straight ahead gaze. Here we studied whether rebound nystagmus changed depending on the kind of eye movement used to reach eccentric gaze (single saccade, small saccades or pursuit) or on the type of eccentric target (briefly flashed vs. continuous). We recorded eye movements of 6 subjects in darkness looking at a red laser dot target was rear-projected at 135 cm, which was on continuously or flashed for 10ms every 500ms. In experiment 1, subjects fixated a central flashing target for 5s, then the target jumped to ±40° and flashed or stayed on continuously for 30s, then moved back to central position where it flashed for 15s. Experiment 2 was similar but the peripheral target was always flashing and the ±40° eccentric positions were reached with smooth pursuit (4°/s), single saccades (40°), or step

saccades (ten 4° jumps). In all conditions the time moving towards the target and the time at the target added to 30s. Subjects performed 5 trials of each condition towards each side. We found that rebound nystagmus was more pronounced with a continuous peripheral target than a flashing target (3.2 vs 2.4 °/s) and that it did not depend on how the eyes reached the peripheral target. Additionally, the intensity of the rebound nystagmus decreased across trials with a difference of more than 1 deg/s between first fifth trial. In some subjects, we observed a significant asymmetry with large or almost absent rebound depending on the direction of eccentric gaze holding, and also that the direction of the nystagmus could reverse during central fixation. Rebound nystagmus offers an opportunity to study the adaptive mechanisms of the gaze holding networks. Because the continuous target generated a more robust rebound nystagmus, we hypothesize that a retinal slip (i.e., velocity) signal is at least partially responsible for rebound nystagmus. The brief flashes do not allow sensing of any retinal slip but the continuous target does. We also showed that rebound nystagmus did not depend on the type of eye movement used to reach the target. Future experiments and modeling studies will determine the relative contribution of velocity vs. position signals in rebound nystagmus.

Disclosures: **J. Otero-Millan:** None. **A. Colpak:** None. **D.S. Zee:** None. **A. Kheradmand:** None.

Poster

150. Eye Movements

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 150.14/II10

Topic: E.01. Eye Movements

Support: German Research Council EXC307 (CIN - Werner Reichardt Centre for Integrative Neuroscience)

Juniorprofessor Program of the ministry for science, research, and art Baden-Württemberg

Title: An investigation of the neuronal tuning to horizontal eye movements in the oculomotor system of larval zebrafish

Authors: C. BRYSCH[1,2], C. LEYDEN[1,2], *A. B. ARRENBERG[1]
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Abstract: The oculomotor integrator (OI) in the vertebrate hindbrain transforms eye velocity input into persistent position coding output, which plays a crucial role in eye position stabilization. Several studies have recently advanced our understanding of the encoding of

horizontal eye position in the hindbrain OI of teleosts. However, the precise tuning of zebrafish oculomotor neurons to motor variables has not yet been determined. This characterization is necessary for a mechanistic understanding of integrator function and eye position control.
Using broadly expressed nuclear GCaMP6f, we record the calcium signals of hindbrain neurons while monitoring eye movements associated with the optokinetic response (OKR). We developed an optic flow stimulus protocol in which the stimulus velocity and directionality dynamically adjust in order to drive the eyes to a defined target position with varying velocities. This protocol allows us to disambiguate the eye position and velocity components of the recorded neural activity in the oculomotor system. We establish tuning curves for these parameters, resulting in two-dimensional tuning maps. We find neurons almost exclusively tuned to eye position, to slow-phase eye velocity, and also neurons with a mixed coding. The velocity coding neurons are predominantly located between the nucleus abducens and the caudal part of the OI. Horizontal eye position-coding neurons are located in a wide, dorsomedial-to-ventrolateral stripe on both sides of the caudal hindbrain.
We find changes in the population coding of eye position along the rostro-caudal axis, with OI neurons already starting to fire below the null-position of the eyes, earlier than motoneurons. Using a second stimulus protocol, which evokes monocular eye movements, we identified neurons exclusively encoding the motor variables of a single eye (monocular) and other neurons tuned to both eyes (binocular).
We identify the putative positions of (pre-) motor structures such as the OI, velocity encoding structures, burst nuclei and abducens internuclear neurons in an anatomical reference map. Our results provide a basis for further investigation of oculomotor integrator structure and function in the zebrafish hindbrain.

Disclosures: **C. Brysch:** None. **C. Leyden:** None. **A.B. Arrenberg:** None.

Poster

150. Eye Movements

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Program#/Poster#: 150.15/II11

Topic: E.01. Eye Movements

Support: NIH R21/R33

LMN foo Bar

Title: Remediating attention using gaze-contingent video games

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Abstract: Background: In addition to the social, communicative and behavioral triad of symptoms that define Autism Spectrum Disorders (ASD), individuals with ASD have difficulty re-orienting attention quickly and accurately. Similarly, fast re-orienting saccadic eye movements are also inaccurate and more variable in both endpoint and timing in individuals with ASD. The brain circuitry that guides the redirection of spatial attention is shared with the circuitry used to shift gaze. This suggests that gaze-contingent training could be a unique way to improve attention-orienting skill. Control of attention is a basic and critical skill for development of language and social communication and for function in dynamic conditions such as social interaction. **Objectives:** 1) Demonstrate the feasibility of using gaze-contingent video games for low-cost in-home training for high functioning adolescents and adults with ASD. 2) Demonstrate improvement of spatial attention orienting and eye movement behavior after 8 weeks of play on these gaze-contingent games in adolescents and adults with ASD. **Methods:** We designed and deployed PC-based gaze-contingent video games using the Unity game engine and an EyeTribe eye tracker. The games were designed around principles to train fast and accurate attention orienting behavior as well as stable fixation. In addition, the games were designed to be sufficiently engaging and robust for long-term at-home use. Trainees with ASD participated in an 8-week training, flanked by pre- and post-testing of eye movement, attention control and assessment of clinical features that might be improved by successful training of attention and eye movement. Compliance and progress were monitored remotely via a secure file sharing protocol. **Results:** Game systems were robust and easy to use with little or no support. The full 8-week training was completed by 75% and there was significant improvement in spatial attention performance including speed of orienting and attention disengagement. Variability of fixation and eye movement accuracy was reduced. **Conclusion:** We delivered a robust, low-cost, gaze-contingent game system for home use that, in our pilot training sample, improved the attention orienting and eye movement performance of participants in 8 weeks of training. The next steps involve a larger clinical trial to assess the importance of gaze-contingency and the generalization of training to real-world behavior.

Disclosures: L. Chukoskie: None. **J. Townsend:** None.

Poster

150. Eye Movements

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Topic: E.01. Eye Movements

Support: Brain/MINDS from AMED [grant number 15653395]

Title: Functional mapping for the cortical network of active visual exploration in the marmoset

Authors: *T. KANEKO[1,2], H. OKANO[2,1]
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Abstract: Distinctive feature of primate visual system is well-developed fovea, which is the part of the retina with the highest spatial resolution, and the active eye-movements, i.e., saccadic eye-movements, to explorer the visual world. In human and old-world monkeys, it is known that the part of frontal and parietal cortex is dedicated to such an active control of eye-movements. Anatomical studies indicate that such cortical eye-fields also exist in other taxa of primates such as the New World monkeys, however, functional identification is remained to be investigated. The present study aimed to map the cortical eye-fields of the common marmoset (*Callithrix jacchus*), a small New World primate by means of the whole brain fMRI recording. The marmoset performed either visually guided saccades or fixation inside a 9.4T MRI scanner. Visual stimulus was presented via back-projection on a screen located inside the scanner, and eye-movements were recorded at 120Hz by a IR camera with a telescope lens located outside of the shield room. A custom made 8-channel phased array coil was used as a receiver coil. Cortical areas of BOLD activation were inferred from non-linear registration of the marmoset MRI brain atlas. The marmoset learned repeated left and right saccadic eye-movements between two targets separated by below 10 degree in visual angle. It was difficult to train them to perform larger saccades for the task, even though they did show larger saccades during free-viewing condition for a naturalistic visual scene. This range of saccadic eye-movements are much smaller than macaque and human. In frontal cortex, BOLD activation was observed in area 8aV, which is a putative marmoset's FEF, but the activation is more prominent at more ventral posterior regions around are 6Va. BOLD activation was also observed in parietal/occipital region. The LIP showed stronger activation during saccades than fixation but the contrast was more robust around V3a and A19DI, which was slightly posterior to LIP. The present study showed that marmosets saccadic eye-movements is rather limited in amplitude comparing to macaque or human, however the cortical eye-fields exist at two distinctive regions in frontal and parietal/occipital cortex of the marmoset brain as similarly to other primates. The region of the strongest activation was slightly shifted from anatomically defined so called cortical eye-field (i.e., FEF). However, similar phenomenon is also observed in fMRI study of macaque and human. Thus, the current study suggests that core functional architecture of the cortical network for the active visual exploration were shared among anthropoid primate species.

Disclosures: T. Kaneko: None. **H. Okano:** None.

Poster

150. Eye Movements

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Topic: E.01. Eye Movements

Support: The New Energy and Industrial Technology Development Organization (NEDO)

JSPS KAKENHI 15K12129, 16H03297

This research is supported by Brain/MINDS from AMED.

Title: An advanced real-time eye tracking system using a new calibration method for untrained marmosets

Authors: *K. MATSUDA[1], Y. SUGASE-MIYAMOTO[2], K. KAWANO[2], T. KANEKO[3]
[1]Human Informatics Res. Inst., AIST, Tsukuba-Shi, Japan; [2]Human Informatics Res. Inst., AIST, Tsukuba-shi, Japan; [3]RIKEN Brain Sci. Inst., Wako, Japan

Abstract: By adopting an USB3.0 digital camera that provides high sensitivity, high resolution, and high frame rate, we developed a non-invasive and inexpensive eye tracking system. An infrared light illuminates one eye, and its reflected image on the cornea and the black image of the pupil are captured by the camera. The center of the pupil and that of the corneal reflection are calculated and tracked over time. Movement of the head is compensated by the reflection. The gaze vector and pupil size data can be read out by three ways, (1) an ascii file in HDD for off-line analysis, (2) on-line transfer via computer network (TCP/IP), and (3) analog voltage output through a digital-analog converter. The adoption of the WINDOWS10 as the operation system makes this eye tracking system user-friendly. Here, we propose two calibration methods: one for the subjects that are easy to train (human subjects and macaque monkeys) and the other for the subjects that are hard to train (marmosets).
To measure eye movements of human subjects or macaque monkeys that are trained to fixate a small target, we carry out a two-step calibration. Step-1, "passive calibration": when the subject spontaneously moves its eye, the length between the pupil center and corneal curvature center and the offset between the corneal reflection and corneal curvature center are calculated. Using these parameters, the subject's gaze vector is calculated in camera-coordinates. Step-2, "active calibration": when the subject fixates on small stationary targets (at least three, up to nine) on a computer display and shifts its gaze between them, a transition matrix of the gaze vector from camera-coordinates to target-coordinates can be calculated. Thus, after the passive and active calibration, we are able to measure the eye position in target-coordinates.
Since the active calibration is not realistically possible on marmosets, we propose a new "semi-active calibration" (as Step-2) for non-trained subjects. We present a moving facial image of a marmoset as a visual stimulus and record the stimulus motion and the subject's gaze vector in camera-coordinates simultaneously. The gaze vectors corresponding to the locations of the stimulus are used to calibrate the eye position in target coordinates. The time required for the calibration is less than 1 minute. Because of the high frame rate of the digital camera, the sampling rate of the system can be as high as 700Hz and the latency of the system less than 4ms. The program is available at https://staff.aist.go.jp/k.matsuda/iRecHS2/.

Disclosures: K. Matsuda: None. **Y. Sugase-Miyamoto:** None. **K. Kawano:** None. **T. Kaneko:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

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Program#/Poster#: 151.01/II14

Topic: E.02. Cerebellum

Support: Wellcome trust grant

Title: Interactions between cerebellum and primary motor cortex during sleep

Authors: *W. XU[1], F. DE CARVALHO[2], A. CLARKE[2], A. JACKSON[3]
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[3]Newcastle Univ., Newcastle-upon-Tyne, United Kingdom

Abstract: Both sleep and the cerebellum are heavily implicated in motor learning. Little is known about cerebellar activity during sleep and even less is known about the dialogue between the cerebellum and the neocortex - which we postulate to occur in order for sleep-dependent motor learning to take place. In this study we investigate the relationship between the cerebellum and the primary motor cortex during natural sleep and compare it to waking free behaviour. We made chronic recordings of local field potentials (LFP) and single unit discharges the cerebellum and the contralateral motor cortex in freely behaving macaques using a wearable device. We find that putative cerebellar Purkinje cells have lower spiking rates during slow wave sleep and higher spiking rates during non-slow wave sleep. Moreover there is coherence between cerebellar and M1 spikes and LFPs that varies as a function of sleep phase. During slow wave sleep there is strong coherence at low frequencies (<1 Hz and delta range) between M1 and cerebellar neurons and LFPs. During non-slow wave sleep there is increased coherence at the 10-15Hz range (spindle frequency) between M1 and the cerebellum in both spiking and LFP signals. Moreover the 10-15Hz coherence between M1 and cerebellum is stronger during sleep than during waking. These result suggest that there is a particular dialogue between M1 and the cerebellum at spindle frequency that becomes enhanced during the parts of sleep that include REM sleep.

Disclosures: W. Xu: None. **F. De Carvalho:** None. **A. Clarke:** None. **A. Jackson:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

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Topic: E.02. Cerebellum

Support: F31 NS096887-02

Title: The rubrocerebellar feedback pathway and cerebellar nuclear output

Authors: *C. S. BEITZEL[1], S. M. LEWIS[2], A. L. PERSON[2]
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Abstract: Understanding the mechanisms of cerebellar output computations requires a clearer understanding of afferents to the cerebellar nuclei. Recent anterograde tracing work from our lab corroborated retrograde tracing studies indicating that the magnocellular red nucleus (RNm) projects to the IN to the near exclusion of the cerebellar cortex, singling out the IN as an independent processing hub. Further, RNm is in a key position to provide motor efferent information to the cerebellum, satisfying predictions about the use of corollary discharge (CD) in cerebellar computations. We explored this feedback loop, both anatomically and physiologically. With the use of dual-virus retrograde tracing, we confirmed that RNm inputs innervating the IN are collaterals that of rubrospinal neurons (n=4). Using monosynaptic rabies tracing, we find that RNm afferents contact premotor output and GABAergic neurons, suggesting RNm activity may play a complex role in IN activity modulation. Additionally, we took advantage of viral mediated expression of Channelrhodopsin to investigate the physiological relationship between these RNm-IN feedback loop. In acute brain slice recordings, optogenetic activation of RNm axons in IN evoked EPSCs (n=5), including slower tonic excitatory currents (n=8). To relate synaptic strength with the capacity of the afferent to drive activity in the IN, we delivered trains of light stimuli in current clamp mode. In neurons that showed a significant response to 50 Hz light trains, firing rates increased 13.1% ± 6.6% (n =12). Furthermore, regression analysis revealed a strong relationship between the tonic current amplitude and the capacity of RNm inputs to drive increases in firing rates (R^2=0.94). Optogenetic activation of IN inputs to RNm revealed strong, direct excitation but no inhibition of RNm neurons (n=10). This electrophysiological result supports our anatomical findings that IN inputs to RNm target regions absent inhibitory somata. Together these data are interesting in light of the idea that the cerebellar nuclei are modulated independent of cerebellar cortex, potentially serving diverse roles in cerebellar mediated motor control.

Disclosures: C.S. Beitzel: None. **S.M. Lewis:** None. **A.L. Person:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: The McKnight Foundation to ALP

Title: Investigating the role of cerebellar output during skilled motor behavior

Authors: *M. I. BECKER, A. L. PERSON
Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Recent electrophysiological evidence suggests that cerebellar neurons predictively encode the velocity of ongoing movements. However, our understanding of how cerebellar kinematic encoding is utilized by the motor system remains limited. We sought to test the role of the cerebellum during unconstrained reach behavior in mice by manipulating activity in the cerebellar nuclei, the sole output structure of the cerebellum, and measuring the effects on movement kinematics. Techniques used previously to manipulate cerebellar nuclear activity, such as electrical stimulation or pharmacological lesions, were limited by a lack of temporal precision, control of sensorimotor context, and cell-type specificity. To implement brief, temporally precise, cell-type specific manipulation of cerebellar output that is tied directly to motor behavior, we developed a kinematic closed-loop (kCL) system for optogenetics, which triggers stimulation based on the real-time kinematics of unconstrained reach behavior in mice. Excitation of cerebellar output neurons resulted in consistent effects on movement kinematics. Stimulated reaches displayed a clear reduction in velocity during and after stimulation compared to control reaches. These alterations in reach velocity were accompanied by positional changes, including a decrease in reach extent in the direction of the target (Wilcoxon rank sum, $p<0.0001$). In addition, stimulated reaches displayed a lower success rate in obtaining the pellet, demonstrating a functional relationship between velocity regulation and endpoint accuracy (Fischer's exact test, $p<0.05$). Next, we tested whether observed kinematic effects were dependent on the sensorimotor context of stimulation. kCL Excitation at three unique kinematic landmarks during outreach (early, middle, and late in the reach trajectory) resulted in a consistent decrease in reach velocity regardless of kinematic location, supporting a context-independent function of cerebellar output during reaching movements. Incorporation of these results with electrophysiological studies has implications for the major algorithmic theories of cerebellar function, including the hypothesis that cerebellar output represents a forward model for state estimation.

Disclosures: M.I. Becker: None. **A.L. Person:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: R01NS050808-05A1

1R01NS079750-01A1

Title: Cerebellar modulation of prefrontal cortex

Authors: *A. SCHOTT[1], I. CARTA[2], C. H. CHEN[2], K. KHODAKHAH[3]
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Abstract: Though the cerebellum is best known for its role in motor coordination, many of its outputs project to non-motor structures. Our laboratory has found evidence of a functional monosynaptic pathway from the deep cerebellar nuclei (DCN) to the ventral tegmental area (VTA), an area critical for reward and motivation. In turn, the VTA has a strong bidirectional connection with the prefrontal cortex (PFC). This mesocortical pathway is thought to be involved in cognition and emotional responses. Here, we investigated the anatomical details of the cerebello-VTA pathway, and determined whether the cerebellum communicates with the prefrontal cortex through the VTA. To trace these connections, we used a GFP-tagged strain of herpes simplex virus type 1, called H129. H129-GFP is a trans-synaptic, non-diluting anterograde tracer. Bilateral injection of H129-GFP into the dentate and interposed DCN of mice results in infection of both VTA and PFC neurons. We also examined the contributions of individual deep cerebellar nuclei to the pathway, by performing single nucleus H129 injections. To test the functionality of these projections, we performed dual *in vivo* extracellular recordings in awake mice. Optogenetic activation of cerebellar axons in the VTA substantially modulates the firing rates of cells in both the VTA and the PFC. These results indicate that the cerebellum provides input to the prefrontal cortex, and may be involved in complex reward-related and cognitive behaviors.

Disclosures: A. Schott: None. **I. Carta:** None. **C.H. Chen:** None. **K. Khodakhah:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Title: Cerebellar inputs to the VTA: Reward and social roles

Authors: *I. CARTA[1], C. H. CHEN[3], A. L. SCHOTT[2], S. DORIZAN[4], K. KHODAKHAH[1]
[2]Neurosci., [1]Albert Einstein Col. of Med., Bronx, NY; [3]Harvard, Boston, MA; [4]Northwestern Univ., Chicago, IL

Abstract: The cerebellum is an important structure for movement. However, some of its projections terminate in brain areas that are not related to movement. Cerebellar fibers are found throughout the midbrain, including the ventral tegmental area (VTA). The VTA, through dopaminergic signaling, participates in reward, motivation and socially related behaviors. We hypothesized that a cerebellar-VTA (Cb-VTA) connection might be a substrate for cerebellar modulation of nonmotor behaviors. To test this, we first examined the functional properties of this connection by expressing Channelrhodopsin2 (ChR2) in the deep cerebellar nuclei (DCN) and recording from the VTA either in vitro or in vivo while stimulating ChR2+ axons from the cerebellum. We found that responses in the VTA were common, and many of these cells were dopaminergic. In order to determine whether the cerebellar input to VTA is important to influence these complex behaviors we expressed either ChR2 or Archaerhodopsin (ArchT) in the DCN of mice, and bilaterally implanted optical fibers above VTA. We then performed behavioral testing to assess sociability and reward. In the three chamber social task, we found that the natural preference of mice for social contexts decreased if the Cb- VTA connection is silenced during the task. Social preference also decreased if stimulation of the Cb-VTA connection is paired with the non-social compartment. In a simplified self-stimulation test we found that mice optogenetically self-stimulated cerebellar inputs to VTA. Moreover, stimulation of the Cb-VTA pathway induced Conditioned Place Preference in the same mice. To test whether the Cb-VTA pathway is naturally active during social behavior, we injected some mice with GCamp6 in DCN and implanted them with optic fibers in the VTA to monitor axonal calcium concentration. We then tested them in the three chamber social test. We observed an increased axonal activation while the mice were close to the social cue. Our data suggest that cerebellum might be an important upstream structure that shapes VTA response to salient stimuli thereby influencing reward and social behavior.

Disclosures: I. Carta: None. **C.H. Chen:** None. **A.L. Schott:** None. **S. Dorizan:** None. **K. Khodakhah:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: NIH 1R01MH093727

Title: Challenging the strict closed-loop organization of olivocerebellar circuits

Authors: *G. J. WOJACZYNSKI, J. F. MEDINA
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: A prevailing theory of cerebellar anatomy and function is that the inferior olive and cerebellum are reciprocally connected into a series of topographically closed-loop circuits. Support for this theory comes from experiments demonstrating that clusters of neighboring Purkinje cells can modulate their own climbing fiber inputs via their projections to nucleo-olivary neurons in the deep cerebellar nuclei (DCN). However, we do not know if the circuit organization is strictly closed-loop, or if there is crosstalk between different loops. To reveal the functional architecture of the olivocerebellar circuit we made small, iontophoretic infusions of the bidirectional tracer Cholera Toxin Beta subunit (CTβ) into a region of the anterior interpositus of the mouse DCN that is necessary for performing classically conditioned eyelid movements. In line with previous studies, Purkinje cells innervating the eyeblink region of the interpositus were in the 5− zebrin band of the cerebellar cortex. In rostral sections these Purkinje cells were found deep in the fissure between lobules V and VI and in caudal sections were found in lateral Crus I. Consistent with a closed-loop organization, these Purkinje cells were all innervated, without exception, by CTβ-labeled climbing fibers arising primarily from the dorsal accessory nucleus of the inferior olive. However, contrary to our expectation, rostral and caudal to labeled Purkinje cells, we found many more labeled climbing fibers within the same 5− zebrin band that did not make contact with a corresponding retrogradely labeled Purkinje cell. The extent of territory of cerebellar cortex innervated by these “orphan” climbing fibers rivaled that of the cortical territory containing labeled Purkinje cells. This finding challenges the conceptual framework of the olivocerebellar system as a series of strictly closed loop circuits, suggesting that climbing fiber signals from the same functional subdivision of the inferior olive are broadcasted to a large population of Purkinje cells that contribute to different aspects of learned behaviors.

Disclosures: G.J. Wojaczynski: None. **J.F. Medina:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

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NIH 1R21AA025572

Title: Transient stimulation of inhibitory cerebello-olivary terminals causes extinction of conditioned eyelid responses

Authors: *O. A. KIM, J. F. MEDINA
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Abstract: During eyeblink conditioning, cells in the inferior olive are inhibited below their baseline rate when an expected aversive airpuff to the eye fails to occur. In current theories of cerebellar learning, this reduction in activity signals a negative prediction error that is used to drive extinction of a previously acquired conditioned response (CR - a closure of the eyelid that anticipates the aversive airpuff and serves to protect the cornea). Previous attempts to test this theory by examining the effects of directly inhibiting the inferior olive have been confounded by the low levels of temporal and cell-type specificity inherent to pharmacological manipulations and electrical stimulation. To overcome these technological shortcomings, we used an optogenetic approach to transiently stimulate the axon terminals of inhibitory neurons that project to the inferior olive from a previously identified eyeblink-controlling region of the deep cerebellar nuclei. Mice expressing channelrhodopsin in inhibitory nucleo-olivary (NO) neurons were trained to blink in response to a tone stimulus that was repeatedly paired with an airpuff to the eye. We found that after learning, brief photostimulation of NO terminals at the time of the airpuff presentation led to a gradual extinction of the CR over the course of repeated trials. In contrast, control experiments showed that the same photostimulation did not alter CR performance if it was delivered after the airpuff. Our results suggest that inhibition of the inferior olive at the time of the expected airpuff is sufficient to extinguish conditioned responding, providing insight into general principles about the signals that teach the cerebellum when to suppress behaviors that are no longer adaptive.

Disclosures: O.A. Kim: None. **J.F. Medina:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: NIH 1R01MH093727

Title: The role of the pontine nucleus in generating the novelty and prediction error signals of climbing fibers during eyeblink conditioning in mice

Authors: *S. OHMAE, J. F. MEDINA
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Recently, we reported that the activity pattern of the climbing fibers during cerebellum-dependent eyeblink conditioning in mice has a striking resemblance to the response of dopamine neurons during reinforcement learning tasks. Namely, climbing fibers fire in response to conditioned stimuli (CS) like tones or flashes of light, if those stimuli predict that an aversive periocular airpuff is about to be presented, or if they are novel. The neural circuits that drive these two types of climbing fiber responses to the CS are currently unknown. Here, we examined the role of the pontine nucleus (PN) because this area of the brainstem is essential for conveying CS-related information to the cerebellum. Mice expressing channelrhodopsin (ChR2) in the PN were trained on an eyeblink conditioning task, using direct photostimulation of the PN as the CS and a periocular airpuff as the unconditioned stimulus. We found that climbing fibers were reliably activated by the PN photostimulation after learning, but not before learning when the photostimulation was relatively novel. Our results suggest that there are different neural circuits driving the novelty and prediction error signals of climbing fibers: activation of the PN, perhaps via its projections to the cerebellum, is sufficient for generating the climbing fiber response to stimuli that predict the impending arrival of the aversive airpuff, whereas the novelty response originates in other parts of the brain.

Disclosures: S. Ohmae: None. **J.F. Medina:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 151.09/II22

Topic: E.02. Cerebellum

Support: NIH 1R01MH093727

Title: Cerebellar control of motor synergies for a learned defensive behavior in mice

Authors: *S. A. HEINEY, J. F. MEDINA
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Abstract: High level motor areas of the brain, including motor cortex, are thought to organize their actions into motor synergies—complex, coordinated contractions of multiple, functionally-linked muscles—to simplify the problem of motor control by reducing its dimensionality. The cerebellum is highly interconnected with motor cortex and other motor areas, but it is not known whether it uses a similar organizing principle or instead controls single muscles independently. To address this gap, we targeted a small region of the cerebellar anterior interpositus nucleus (AIN) that is known to be necessary for making eyelid movements during eyeblink conditioning and examined its contribution to the control of a learned defensive behavior.
We trained mice to blink their eye in response to a light conditioned stimulus (CS) that was repeatedly paired with an airpuff to the eye. The mice were head-fixed and stood on a cylindrical treadmill that was free to move under their control. We monitored eyelid position and body movements using two synchronized high speed cameras. We also monitored EMG activity from multiple muscles, including those of the neck and forelimb.
We found that even in this “simple” task, a wide network of muscles spanning multiple body segments were recruited in a complex and coordinated way, suggestive of a functional motor synergy. As the mice learned to close the eyelid in response to the CS, they also developed coordinated activation of neck and limb muscles that on the high speed videos looked like an attempt to escape from the anticipated airpuff. All these coordinated defensive movements were correlated, both in their timing and probability of occurrence on single trials. Electrical microstimulation with low currents (<10 uA) in the eyeblink controlling region of the AIN resulted in similar coordinated movements, and small electrolytic lesions in the same region abolished the previously learned coordinated movements altogether. Our results suggest that, like motor cortex, the cerebellum may use motor synergies to simplify the problem of motor control.

Disclosures: S.A. Heiney: None. **J.F. Medina:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

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Topic: E.02. Cerebellum

Support: CONACYT (BALF 576171)

CUERPO ACADEMICO DE NEUROQUIMICA (UV-CA-304)

CUERPO ACADEMICO DE NEUROCIENCIAS (UV-CA-28).

Title: The number of active purkinje neurons decreases while the distance between them increase with sexual experience in male rats

Authors: *B. A. LARA[1], J. SANCHEZ-RODRIGUEZ[1], J. MANZO[2], M. E. HERNANDEZ[2], L. I. GARCIA[2], G. ARANDA-ABREU[2], G. A. CORIA-AVILA[2], R. TOLEDO-CARDENAS[2]
[1]DOCTORADO EN INVESTIGACIONES CEREBRALES, UV, XALAPA, Mexico; [2]CENTRO DE INVESTIGACIONES CEREBRALES, UV, Xalapa, Mexico

Abstract: The cerebellum is a structure that associated to multiple functions such as mobility, learning processes, verbal fluency, motor, and sexual behavior. In the latter many authors have described it suggesting that there is an activation of the cerebellum during sex development. Nevertheless it has not been described what happens on the Purkinje layer, that is a key in the cerebellar circuitry. c-Fos and Calbindin immunoreactivity was observed on the Purkinje layer of de cerebellar vermis following tests of sexual behavior. Tests consisted in introducing a male with previous sexual experience to a socialization arena with a receptive female. After ejaculation, the male was retired from the area and maintained in an acrylic box for 60 minutes. In the experimental session and depending on their group, males were submitted to one, two, three, and four ejaculations. Then, males were anesthetized with sodium penthobarbital and the obtained tissue was affixed in paraformaldehyde for a posterior analysis. The number of Purkinje cells immunoreactive to c-Fos and Calbindin decreased significantly in the fourth ejaculation group in comparison with the control and one ejaculation groups. Also, an increment was observed in the distance between Purkinje cells as the ejaculation increased. As results suggest, during acquisition of sexual experience several Purkinje cells of the cerebellum are necessary to learn and improve the execution of this behavior. However, as the animal becomes expert fewer neurons are necessary to execute optimal behavior; whether these neurons actually separate among them is a subject of further research.

Disclosures: B.A. Lara: None. **J. Sanchez-rodriguez:** None. **J. Manzo:** None. **M.E. Hernandez:** None. **L.I. Garcia:** None. **G. Aranda-abreu:** None. **G.A. Coria-avila:** None. **R. Toledo-cardenas:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: NIH F31-NS089303

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NIH U01-NS090541

Title: Combined transsynaptic tracing and activity mapping of cerebellum-to-forebrain pathways

Authors: *T. J. PISANO[1,2,3], M. KISLIN[1], D. E. BAKSHINSKAYA[1], S. DEIVASIGAMAN[1], J. C. LEE[1], R. E. AGUILAR[1], *J. N. KATES-HARBECK[4], B. DEVERETT[1,2,3], E. A. ENGEL[1], L. W. ENQUIST[1,2], S. S.-H. WANG[1,2]
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Abstract: Clinical evidence suggests that the cerebellum contributes to non-motor functioning. However, understanding the mechanism of these contributions is hampered by the absence of a comprehensive cerebello-thalamo-neocortical output atlas. The cerebellum's connectivity to the rest of brain is made difficult by the fact that long-distance pathways project polysynaptically through the deep nuclei. Functional MRI shows covariations in activity between cerebellum and neocortex (Buckner et al. 2011, *J. Neurophysiol* 106:2322), but these measurements lack spatial resolution and do not reveal the directionality of influence.
Transsynaptic tracing provides a powerful tool for tracing long-distance pathways. We have created a high-throughput pipeline for efficient long-distance tracing between cerebellum and the rest of the brain, using an anterograde-spreading variant of herpes simplex virus H129 (HSV-H129), iDISCO-based tissue clearing, and light-sheet microscopy (LaVision Biotec., Bielefeld, Germany). We have performed over 75 injections to create a library of brains, each with a different pattern of HSV-H129 injection. We are now developing software analysis tools for automated analysis and a convolutional neural network for detecting immunohistochemically-labelled cell centers and registering the data to the Allen Brain Atlas. This software is compatible both with mid-performance desktop computers and high-performance computing clusters. Using this pipeline we have achieved quantitative mapping of most of the posterior cerebellar cortex output to disynaptic midbrain targets and trisynaptic neocortical targets.
To associate viral tracing with function, we are now performing brain-wide mapping of activation of the immediate early gene c-Fos after optogenetic silencing of Purkinje cells. Analysis using ClearMap (Renier et al. 2016 *Cell* 165.7:1789) shows that optogenetic inhibition of cerebellar cortex, which removes long-distance inhibition by Purkinje cells, leads to increases in midbrain and forebrain activity relative to controls. We are now comparing anterograde viral tracing with c-Fos data to quantify the relationship between tracing and activity.

Disclosures: T.J. Pisano: None. **M. Kislin:** None. **D.E. Bakshinskaya:** None. **S. Deivasigaman:** None. **J.C. Lee:** None. **R.E. Aguilar:** None. **J.N. Kates-Harbeck:** None. **B. Deverett:** None. **E.A. Engel:** None. **L.W. Enquist:** None. **S.S. Wang:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Support: New Jersey Brain Injury Research Fellowship CBIR16FEL010

NIH R01 NS045193

Nancy Lurie Marks Family Foundation

Title: Disrupted cerebellar neural activity in development on neocortical dendritic structure and non-motor behaviors results in altered neocortical dendritic morphology

Authors: *J. VERPEUT[1,2], A. TAO[1,2], A. BADURA[4], T. D. PEREIRA[1], L. TAO[1], E. C. COPE[1,3], B. A. BRIONES[1,3], E. GOULD[1,3], S. S.-H. WANG[1,2]
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Mol. Biol., [3]Psychology, Princeton Univ., Princeton, NJ; [4]Netherlands Inst. For Neurosci., Amsterdam, Netherlands

Abstract: The cerebellum is among the most-often-reported sites of abnormality in autism spectrum disorder (ASD), yet adult injury to the cerebellum does not lead to ASD. We are testing the hypothesis that cerebellar activity during development influences the development of flexible behavior and the maturation of neocortical circuitry. First, we tested for distal effects of cerebellar perturbation using heterozygous L7-tuberous sclerosis 1 (Tsc1) mice, in which Purkinje cell (PC) firing is specifically attenuated, and which display abnormal social interactions and impaired reversal learning. Using biolistic labeling with DiI, we found that spines in pyramidal neurons of prelimbic layer II/III had increased density in basal (+6.7 ± 2.4 spines/10 µm, 28.9 ± 1.6 spines/10 µm, N=8 mice) dendrites compared to wild-type littermates (22.3 ± 1.8 spines/10 µm, N=8 mice), consistent with the hypothesis that decreases in PC spike output cause long-term increases in neocortical spine density. In a second set of experiments, we used Designer Receptors Activated Exclusively by Designer Drugs (DREADDs) to increase PC spike output in specific lobules during postnatal development. We used an adeno-associated virus (AAV8-hSyn) carrying sequence for the inhibitory DREADD hM4Di, fused to mCherry protein under a synapsin-1 promoter to drive expression in molecular layer interneurons of lobule VI in thy1- yellow fluorescent protein (YFP)-expressing mice (YFP-H line). After treatment with the DREADD agonist clozapine-N-oxide (CNO) from postnatal day 21-60, mice showed greater variation in social preference than control (N=20 mice DREADD, 43 mice control; $p<0.05$, chi-square comparison of variance). We are now investigating the relationship between alterations in behavior, the distribution of DREADD expression, and the degree of perturbation to neocortical pyramidal dendrites.

Disclosures: **J. Verpeut:** None. **A. Tao:** None. **A. Badura:** None. **T.D. Pereira:** None. **L. Tao:** None. **E.C. Cope:** None. **B.A. Briones:** None. **E. Gould:** None. **S.S. Wang:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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CONACyT Grant LVC575913

CA-28-Neurociencias

CA-304-Neuroquímica

Title: Fos expression in cerebellar hemispheres induced by olfactory stimulation of male rats during training for sexual experience

Authors: *Z. S. HERNANDEZ BRIONES[1], L. VASQUEZ-CELAYA[1], P. CARRILLO[2], A. J. MARTINEZ-CHACON[2], R. TOLEDO[3], M. E. HERNANDEZ[3], G. A. CORIA-AVILA[3], J. MANZO[3], L. I. GARCIA[3]
[1]Doctorado en Investigaciones Cerebrales, UV, Xalapa, Mexico; [2]Inst. de Neuroetología, UV, Xalapa, Mexico; [3]Ctr. de Investigaciones Cerebrales, Xalapa, Mexico

Abstract: Multiple functions have been attributed to the cerebellum: coordination, planning, control of intentional and spontaneous movements, regulation of posture, vestibular function, cognitive, perceptive and emotive processes, sex and orgasm. Previously we showed that in non-contact experiments, olfactory stimulation and the acquisition of sexual experience generate changes in the expression of Fos at the cerebellar cortex, in different cellular layers such as the granular and Purkinje as well as in the deep cerebellar nuclei. The aim of present work is to analyze and compare the expression of Fos protein in granular and Purkinje layer in the cerebellar hemispheres of male rats during the acquisition of experience for sexual behavior (5 trials). Male Wistar rats (250-350 gr) were used and olfactory stimulation was provided 24 hours after each session of sexual behavior training. Every test lasted 70 min in which an experimental rat was placed in a cubic acrylic chamber (30 × 30 × 60 cm) with a double bottom. The lower compartment contained a bowl filled with clean woodshaving as control (Ctrl), or sprayed with almond scent (Alm) or urine from receptive females (Rf). At the end of the test rats were deeply anesthetized with sodium pentobarbital (60 mg / kg, i.p) and transcardial perfusion was carried out. The cerebellar hemispheres was obtained and processed with an immunohistochemical reaction for Fos protein. Data demonstrate the effect of olfactory stimulation and changes in the

activation of the lobes Sim a, Sim b, Crus I and Crus II to the different odors, mainly with the receptive female stimulus. Thus we suggest that there are lobes that specifically participate in the processing of olfactory signals associated with rewarding experiences and that are part of processes of memory and learning.

Disclosures: Z.S. Hernandez Briones: None. **L. Vasquez-Celaya:** None. **P. Carrillo:** None. **A.J. Martinez-Chacon:** None. **R. Toledo:** None. **M.E. Hernandez:** None. **G.A. Coria-Avila:** None. **J. Manzo:** None. **L.I. Garcia:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: CONACyT (ZSHB326816)

CA-28-Neurociencias

SNI LELV

Title: Fastigial nucleus Fos-ir activation induced by olfatory stimulation in male rats

Authors: *P. B. HERNÁNDEZ[1], L. E. LANDA[1], N. CARLOS[1], Z. S. HERNANDEZ-BRIONES[2], L. VASQUEZ-CELAYA[2], P. CARRILLO[3], G. A. CORIA-AVILA[4], J. MANZO[4], L. I. GARCIA[4]
[1]Facultad De Medicina, UV, Xalapa, Mexico; [2]Doctorado en Investigaciones Cerebrales, UV, Xalapa, Mexico; [3]Inst. de Neuroetología, UV, Xalapa, Mexico; [4]Ctr. de Investigaciones Cerebrales, UV, Xalapa, Mexico

Abstract: Previous studies in male rats have shown that in each lobe of the cerebellar vermis both sexual arousal by distand receptive females (non-contact sexual stimulation) and sexual experience acquisition modifies Fos-ir expression in granule and Purkinje layers. Hence, we consider necessary the further analysis in those cerebellar nuclei since are the efferent pathway of the information integrated in the cerebellar cortex. Therefore, the aim of this study was to analyze Fos expression in the fastigial nucleus. Male rats in different sexual behavior training stages were exposed to odors of almond scent or urine from receptive females. Olfactory stimulation was performed 24 hrs after the execution of 1, 3 and 5 sexual behavior training sessions. The stimulation lasted for 70 minutes and them rats were deeply anesthetized with sodium pentobarbital (60 mg / kg, i.p) and transcardiac perfusion was carried out. The cerebellar vermis was obtained and processed with an immunohistochemical reaction for Fos protein. The results show increased Fos-ir expression in the group stimulated with woodshaving more urine

from receptive females in comparison with almond (woodshaving sprayed with almond scent) and control (clean woodshaving) groups. Similarly, the acquisition of sexual experience increases Fos-ir expression in all groups, but expert subjects (5 sessions) show a higher average of inmureactivity cells. We conclude that the number of Fos-ir cells at the fastigial nucleus of cerebellar vermis increases as experience in sexual behavior is gained. Such activation depends on sensory and/or motor learning, generated by repeated exposure to stimuli associated with rewarding events like copulation. The number of neurons activated by olfactory stimulation with odorants increases, compared with the control group. Sexual experience as well as olfactory stimulation with odorants generates cerebellar plasticity themselves, so that a synergistic effect is obtained when the two learning occurs simultaneously.

Disclosures: P.B. Hernández: None. **L.E. Landa:** None. **N. Carlos:** None. **Z.S. Hernandez-Briones:** None. **L. Vasquez-Celaya:** None. **P. Carrillo:** None. **G.A. Coria-Avila:** None. **J. Manzo:** None. **L.I. Garcia:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: NIH NS079750

Title: The subthalamic nucleus communicates with the cerebellum

Authors: *R. BHUVANASUNDARAM, K. KHODAKHAH
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The subthalamic nucleus and the cerebellum are two subcortical motor structures, which have also been suggested to have non-motor functions. The aim of the current study was to elucidate the organization and functional properties of a di-synaptic pathway between subthalamic nucleus and the cerebellum in mice. The previous study in primates implicated pontine nuclei or pedunculopontine tegmental nuclei as an intermediate between subthalamic nucleus and the cerebellum. We examined whether inputs from the subthalamic nucleus modulate activity in the pontine nuclei. Optogenetic stimulations of the subthalamic axons in the pontine nuclei of awake head-restrained mice elicited responses in about half of recorded cells in the pontine nuclei, with a latency of 2-4 milliseconds. To determine how robustly subthalamic nucleus conveys information when repeatedly activated, we examined the response of pontine neurons to 20 Hz train of stimulation. We found that the subthalamic-pontine pathway remained effective at this frequency. We next examined whether subthalamic nucleus sends projections to the cerebellum via pontine nuclei. By injecting anterograde herpes simplex trans-synaptic viral

tracer in subthalamic nucleus we found that in the cerebellum the second-order expression was present in the posterolateral portion of the Crus II and paramedian lobule, along with expression in the vermal part of lobules VI and VII. GFP positive neurons were also present in the fastigial, interposed and the dentate nuclei. First-order expression was apparent in the medial and lateral portion of the pontine nuclei. Based on our electrophysiological and anatomical examinations we propose that the subthalamic nucleus sends strong functional projections to the pontine nuclei, which then propagates to the cerebellum.

Disclosures: R. Bhuvanasundaram: None. **K. Khodakhah:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

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Topic: E.02. Cerebellum

Support: UTHSC College of Medicine

UTHSC Neuroscience Institute

UTHSC Department of Anatomy and Neurobiology

Title: Cerebellar Purkinje cell simple spike activity represents phase differences between neuronal oscillations in the medial prefrontal cortex and hippocampus

Authors: *S. S. MCAFEE[1], Y. LIU[1], R. V. SILLITOE[2], D. H. HECK[1]
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Abstract: The cerebellum was long perceived as an exclusively motor-related structure, but it is now widely recognized for its involvement in cognition, in both experimental animal models and humans. Imaging studies have described distinct cerebellar activation patterns that are correlated with the performance of specific cognitive tasks. For example, activation of the lobulus simplex has been strongly linked to the performance of spatial working memory tasks (Desmond et al., 1997). However, a neuronal mechanism for how the cerebellum is involved in cognition has yet to be identified.
There is broad consensus that the cerebellum plays a key role in several tasks involving precise timing, such as the temporal coordination of movements, the perception of temporal patterns and predictive timing related to learning. Research on the role of the cerebellum in timing has focused almost exclusively on sensorimotor tasks. Here we asked whether the concept of cerebellar timing function might be usefully applied in the search for neuronal mechanisms underlying cerebellar cognitive function. A form of precise temporal coordination associated

with cognitive function is the task-related modulation of coherence between two structures. An increase in the coherence of oscillations has been suggested as a mechanism to enhance neuronal communication (Fries, 2015). The medial prefrontal cortex (mPFC) and dorsal hippocampal CA1 (CA1) region show increases in coherence during spatial working memory tasks, which are also known to require an intact cerebellum.
Here we report that Purkinje cell (PC) simple spike activity in cerebellar lobulus simplex in awake, head-fixed mice is correlated with specific phase differences between local field potential oscillations that were simultaneously recorded in the mPFC and CA1. Most PCs represented phase differences in more than one frequency band and within the sample of 30 PCs analyzed here phase differences in all standard frequency bands (delta, theta, beta and gamma) were represented. These findings suggest an involvement of the cerebellum in measuring and/or coordinating phase relationships between the mPFC and CA1. We hypothesize that these findings are indicative a novel neuronal mechanism for cerebellar involvement in cognitive function by coordinating the phase relationships of oscillatory neuronal activity in communicating brain structures.
Desmond et al. (1997) J. Neurosci. 17:9675-9685.
Fries P (2015) Neuron 88:220-135.

Disclosures: **S.S. McAfee:** None. **Y. Liu:** None. **R.V. Sillitoe:** None. **D.H. Heck:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Program#/Poster#: 151.17/JJ3

Topic: E.02. Cerebellum

Title: A paired optogenetic and functional MRI method for defining region-specific connectivity between the cerebellar cortex and forebrain

Authors: C. F. SANCHEZ[1], K. CHOE[2], T. S. OTIS[4], N. G. HARRIS[3], *P. J. MATHEWS[5]
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Abstract: Previous evidence suggests that discrete regions of the cerebellar cortex are functionally connected with the forebrain, mediating long-range communication potentially important for several motor and non-motor behaviors; however, the connectivity map remains incomplete owing to the technical challenge of surveying the activity of the entire forebrain while eliciting discrete patterns of cerebellar output. To establish a map of functional connections between defined regions (anatomical or functional) of the cerebellar cortex and forebrain we have combined optogenetic and fMRI (ofMRI) methods in mice. Using optogenetics we selectively modulated a region of the cerebellar cortex near folia V/VI of the

simplex lobule capable of driving cerebellar output. By light stimulating this region in either a L7-Cre/+; Archaerhodopsin-GFP/+ (Arch) or L7-cre/+ (control) mouse we could reliably induce forelimb movement, consistent with our prior report (Lee, Mathews et al., 2015). We paired this with brain-wide functional magnetic imaging using a 7T Biospec small animal MRI system. T2-weighted structural scans were acquired with a RARE sequence followed by a series of whole-brain GE-EPI functional scans, during which 10 cycles of 30 second laser pulse trains at 50% duty cycle were delivered. Image processing and statistical analyses were performed with FSL. By varying stimulation frequency or light intensity (5, 10, 20 Hz at 20 mW; 5, 10, 20 mW at 5 Hz, respectively) we found that 20 mW, 5 Hz light stimulation of Arch (n=5) vs. control (n=6) mice induced the most reliable, statistically significant ($p<0.001$) increase in BOLD signal in motor-related forebrain structures. No significant increases were induced by light stimulation at 10 and 20 Hz. At a fixed 5 Hz stimulation frequency, intensities of 5 and 10 mW resulted in significantly fewer activated voxels (threshold of $P<0.001$/voxel) compared to 20 mW across multiple brain regions. Using 5 Hz/20 mW laser stimulation as standard parameters, brain-wide quantification revealed robust and significant BOLD signal increases in motor areas of the forebrain including the thalamus and motor cortex as well as non-motor areas like the hippocampus and anterior cingulate cortex (Arch (n=10) > control (n=9); $p<0.001$). We further validated these regions of activation with *in vivo* recordings using custom designed multi-electrodes and c-Fos immunostaining (n=3). These results validate the use of the ofMRI method for cerebellum-forebrain functional connectivity mapping, and provide a new tool for investigating mouse models of cerebellar related neurological diseases.

Disclosures: C.F. Sanchez: None. **K. Choe:** None. **T.S. Otis:** None. **N.G. Harris:** None. **P.J. Mathews:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Program#/Poster#: 151.18/JJ4

Topic: E.02. Cerebellum

Support: KAKENHI 16K070025

Title: Single axon morphology of the spinocerebellar projection in the mouse

Authors: *I. SUGIHARA[1], Y. LUO[2]
[1]Tokyo Med. & Dent. Univ. Grad. Sch. Med., Tokyo, Japan; [2]Systems Neurophysiol., Tokyo Med. & Dent. Univ., Tokyo, Japan

Abstract: The ascending projection systems from the spinal cord to the cerebellum have an essential role in sensorimotor coordination in various movements of limbs and trunk. The variety

of location of cerebellum-projecting neurons in different laminas and segments of the spinal cord suggests multiple subclasses of the spinocerebellar projection. However, morphological or functional classification of the spinocerebellar projection system has not been much clarified beyond the conventional pathway-related dorsal and ventral projections. In the present study, we labeled spinocerebellar axons anterogradely with biotinylated dextran amine injected into thoracic, lumbar and sacral segments and reconstructed projection patterns of individual single axons including their extra-cerebellar branches from serial sections in the mouse. We reconstructed 23 spinocerebellar axons, completely in the cerebellum and brain stem and partially in the spinal cord. Axonal termination in the cerebellar cortex was plotted upon the expression map of aldolase C (zebrin) on the unfolded scheme of the cerebellar cortex. Major cortical termination patterns of spinocerebellar axons were classified into (1) bilateral vermal lobules I-V type, (2) bilateral vermal lobules I-V and VIII type, (2) unilateral medial paravermal lobules I-V and VIII type. Some axons had collaterals in the spinal cord, medulla (nucleus X, inferior vestibular nucleus and various reticular nuclei) and/or in the medial and anterior interposed cerebellar nuclei. Axonal path was either medullar or pontine before entrance to the cerebellum and was dorsal or ventral in the spinal cord. In relation to the possible origin of axons, Clarke's column neurons and Stilling's nucleus neurons showed particular termination patterns. However, except for these special cases, high variability in the termination pattern of these axons prevent simple classification of axonal projection patterns. The results indicate that the spinocerebellar projection is composed of various heterogeneous types of projecting axons, besides some special groups of axons that have relatively uniform projection patterns.

Disclosures: I. Sugihara: None. **Y. Luo:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

Location: Halls A-C

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Topic: E.02. Cerebellum

Support: NCERC

Title: Spatial organization of pontine and medial spiriform afferents to the oculomotor cerebellum of pigeons (Columba livia)

Authors: *C. GUTIERREZ-IBANEZ, R. M. LONG, D. R. WYLIE
Neurosci. and Mental Hlth. Inst., Univ. of Alberta, Edmonton, AB, Canada

Abstract: In mammals three regions of the cerebellum have been implicated in oculomotor behavior: (1) the oculomotor vermis and paravermis, (lobules V, VI, and VII); (2) uvula and nodulus; and (3) flocculus and paraflocculus. The latter two are collectively known as the

vestibulocerebellum. In birds, extensive studies on connectivity and neural responses have shown the existence of clear analogues of the vestibulocerebellum in pigeons, and a shared role in the control of oculomotor behavior. In contrast, the function of folia V-VII in birds has not been extensively investigated, and little is known about what role it may play in the control of oculomotor behavior. In mammals, the oculomotor vermis and paravermis receives mossy fiber projections from the nucleus reticularis tegmenti pontis and the pontine nuclei, which in turn receive afferents from the superior colliculus, the accessory optic system, and other subcortical visual and oculomotor centers. In pigeons, two nuclei at the base of the pons, the medial and lateral pontine nuclei (PM and PL respectively) have been proposed as homologues to the pontine nuclei of mammals. As in mammals, these nuclei receive several inputs from visual and oculomotor centers, including the optic tectum, the accessory optic system, the pretectum and the ventral thalamus, and send projections to folia V-VII. Additionally, folia V-VII of birds receives projections from the medial spiriform nucleus (Spm) in the thalamus, which receives projections from the telencephalon, including the visual wulst and visual areas of the arcopallium. While is clear that, like in mammals, folia V-VII, receives visual inputs, it is completely unknown how these inputs are organized. Here we used double injections of fluorescent tracers to study the organization of inputs from both pontine nuclei (PM and PL) and Spm to folia VI-VIII of pigeons. Red (Alexa fluor 594) and green (Alexa fluor 488) conjugated cholera toxin subunit B was pressure injected in different cerebellar zones (sensu Arends and Ziegler, 1991) of folia V-VII. Our results show a topographical organization of inputs from the pontine nuclei and Spm to folia V-VII of the pigeon. In the pontine nuclei, injection in the more lateral part of folia V-VII, resulted in retrogradely labelled cells in medial portions of the pontine nuclei, while more medial injections resulted in more lateral labeling. The situation is reversed in Spm, where more medial injections result in labeling on the medial portion of the nuclei and lateral injections label cells more laterally. This is an important first step to understand the role of folia V-VII of the cerebellum of birds in controlling oculomotor behavior.

Disclosures: C. Gutierrez-Ibanez: None. **R.M. Long:** None. **D.R. Wylie:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Topic: E.02. Cerebellum

Support: BBSRC grant BB/J017116/1

Title: The processing of conditioned stimuli during instrumental learning: 7 Tesla event-related functional MRI

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Abstract: Introduction
During instrumental rule learning, participants can learn arbitrary associations between symbolic conditioned stimuli (CS), actions and outcomes through trial and error. A well-known system that controls this learning includes parts of the prefrontal cortex, the hippocampus, the basal ganglia and the cerebellum (Murray & Wise, 2000). However, the contributions of its parts are poorly understood. Our previous 3T fMRI work has shown that areas of the cerebellar cortex (lobule HVIIA) that communicate with the prefrontal cortex are responsive to instrumentally acquired CS (Ramnani, 2006, 2014). Here, we exploited the greater sensitivity and anatomical resolution of ultra-high field 7T event-related fMRI to examine in detail CS-related activity in the rest of this circuitry. We also sought to verify the repeatability of anatomical results across individual participants. We focused on cerebellar and hippocampal activity specifically time-locked to CS.
Methods
Fifteen healthy adult participants (21–39 y; 6 F) underwent 18.5 min of 7T BOLD-weighted fMRI scanning (1.5-mm isotropic voxels; ultra-high resolution structural image also acquired, 0.7-mm isotropic voxels). Data analysis in MATLAB/SPM12: Preprocessing, first- and second-level GLMs. Participants acquired associations between five arbitrary visual CS and each of four right-hand digit movements using trial-and-error learning. CS were followed by a variable delay (0.12–3.85 s), a *Go!* signal and visual feedback (correct/incorrect). Control trials: Same trial structure but visual cues *directly* specified the movement to be executed, so no rules were learned (direct, D).
Results
The frequency of correct responses increased during learning. Activity time-locked to arbitrary CS (vs. D) in error-free trials was present in, among other areas, three specific parts of cerebellar lobule HVIIA. We compared activity time-locked to CS that subsequently resulted in correct <> incorrect decisions. Such differences were found bilaterally in the hippocampus. Our findings were consistent across individuals at the single-participant level.
Conclusions
Our results provide support for the hypothesis that cerebellar circuitry is engaged in the acquisition of cognitive skills (Ramnani 2006, 2014), and we also identify three highly specific areas within lobule HVIIA that are sensitive to CS with associative properties. Also, CS evoke differential responses in the hippocampus depending on whether they result in correct or incorrect responses. This is consistent with the view that hippocampal circuitry plays a role in memory-guided response selection.

Disclosures: M. Mikkelsen: None. **S.A. Hurley:** None. **S. Clare:** None. **N. Ramnani:** None.

Poster

151. Cerebellum Interactions With Other Brain Regions

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Program#/Poster#: 151.21/JJ7

Topic: E.02. Cerebellum

Support: FAPESP 2014/24774-8

CAPES

FAPESP 2016/00557-3

Title: Cerebellar histaminergic system participates in motor and non-motor functions of the cerebellum in mice

Authors: *A. C. GIANLORENÇO[1], E. GUILHERME[1], B. SILVA-MARQUES[1], C. MONICI[1], T. RUSSO[1], R. MATTIOLI[2]
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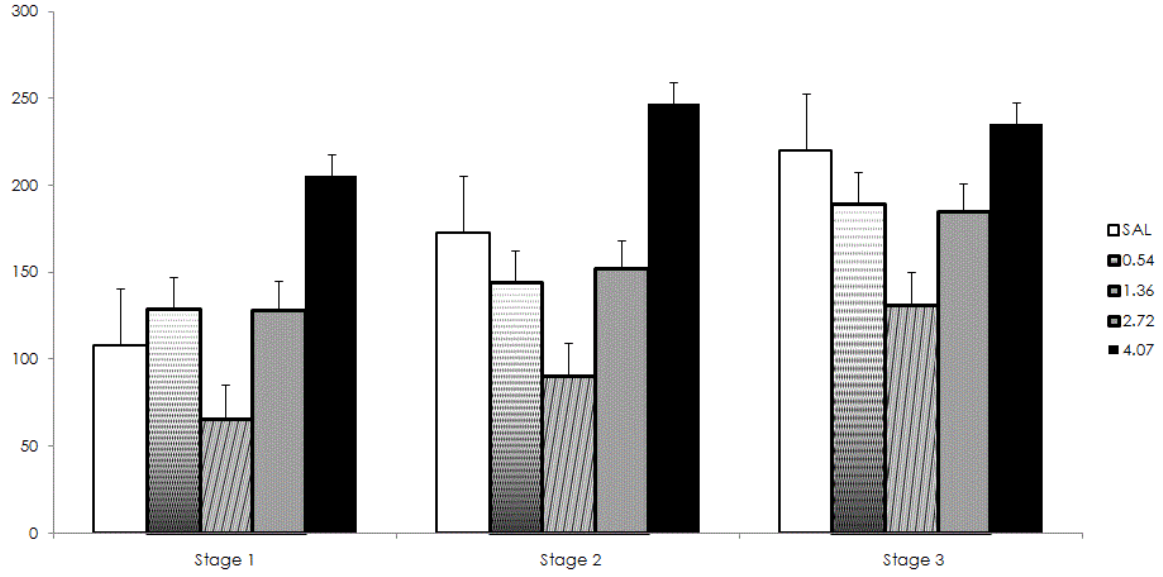
Abstract: The cerebellum is tradicionally related to motor control. However, an increasing amount of evidence has confirmed that the cerebellum is also involved in non-motor functions. Our group has recently found that histaminergic compounds within the cerebellar vermis modulates emotional memory, particularly in fear- anxiety related processes. This study will help us to understand the extended role of the cerebellum in the nervous system, in which cerebellar structure contributes to neuropsychiatric symptoms, even in the absence of motor impairment. The present study investigated the role of cerebellar histaminergic system in motor and non-motor functions in mice. For this end, we performed a series of experiments in which histamine, chlorpheniramine (H1 antagonist receptor), ranitidine (H2 antagonist receptor) and thioperamide (H3 antagonist receptor) were microinjeted into the cerebellar vermis of mice and the animals were submitted to the open field (experiments 1-4) to evaluate anxiety and locomotor activity e rota-rod and balance beam test (experiments 5 and 6) for coordination, balance and motor learning The results showed that chlorpheniramine and thioperamide affected behavior of mice in the open field. While the H1 antagonist produced an increasing of mice activity, the H3 antagonist induced an anxiolytic effect. On the other hand, histamine showed a significant dose-effect on coordination, balance and motor learning in mice submitted to rota-rod. The results showed a possible facilitation of histamine at the highest dose in the evaluation of learning and motor performance in the rota-rod. No significant differences between doses were found on the balance beam, suggesting that cerebellar histaminergic projections can modulate the cerebellar circuit to ensure that movements are performed efficiently. In summary, our data indicates that

cerebellar histaminergic system participates in both motor and non motor functions of the cerebellum in mice.



Disclosures: **A.C. Gianlorenço:** None. **E. Guilherme:** None. **B. Silva-Marques:** None. **C. Monici:** None. **T. Russo:** None. **R. Mattioli:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.01/JJ8

Topic: E.04. Voluntary Movements

Support: Grant support: National Science Foundation BCS-1455866

Title: Assessing performance, role asymmetry, and handedness in physical joint interaction for object manipulation

Authors: *K. MOJTAHEDI[1], Q. FU[1], M. SANTELLO[2]
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Abstract: Most studies of social cognition have focused on individual agents. Recently, the focus has shifted toward human-human interaction or interacting agents. Previous studies have found that dyads performed tasks, ranging from moving a crank together to tracking a cursor using robotic interface, better than individuals alone (Ganesh et al., 2014, 2017; Reed et al.,

2009). These results were based on comparing dual versus unimanual (dominant hand) performance. However, confound may exist in such comparison since the dyadic execution and individual execution of these tasks involves different number of end effectors. Furthermore, a major gap exists regarding how each agent in dyadic physical coordination contributes differently to task execution. Lastly, the extent to which handedness may influence performance and coordination of physical interactions remains unclear. To address these questions, we performed a series of studies (72 right-handed subjects) using a task that required lifting and balancing a U-shaped object. Subjects were randomly paired to perform the task in 4 dyadic conditions using one hand each, or solo conditions where each subject performed the task individually using both hands. Unlike previous work, manipulation performance in dyadic interactions was not better than solo (bimanual) performance. Specifically, dyadic interaction was beneficial only to the worse partner, but not the better partner. This is not consistent with the previous finding that physical coupling is beneficial to both partners in robotic rehabilitation framework (Ganesh et al., 2014, 2017). To assess the role asymmetry in dyadic conditions, we first defined and validated an approach that uses the moment rate to define each agent's role during physical interactions. This was achieved with an additional experiment on 10 dyads where each participant was explicitly assigned with either a leader or follower role (L-F group). We found that the leader exhibited significant greater moment rate than the follower. Interestingly, similar asymmetry was found in the first experiment in which no explicit role was given, but not to the same extent of the L-F group. The results support the notion that role assignment would emerge spontaneously during physical interaction. Handedness had no effect on performance or role emergence. Specifically, we found that all dyadic conditions exhibited similar performance despite of different pairings of dominant and non-dominant hand in the joint actions. Furthermore, the naturally emerged role asymmetry were consistent across all dyadic conditions, suggesting the emerged leader tended to remain as leader regardless of which hand is used.

Disclosures: **K. Mojtahedi:** None. **Q. Fu:** None. **M. Santello:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Support: This work was supported by the GINOP 2.3.2-15-2016-00022 grant

EFOP-3.6.1-16-2016-00004

Measurements were performed at the Pazmany Peter Catholic University, Budapest, Hungary

Title: Body position affects muscle activity variances in the non-dominant arm during arm cycling

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Abstract: Arm cycling movements were performed on a special, self-designed and constructed device that can be utilized both in sitting and laying positions of the cycler. A cohort of 9 right handed, able bodied persons (5 woman, 4 man, 26.3+/-3.2 years) were involved in this study. Each participant took part in 2 sessions (on 2 separate days). At one of the occasions the participant arm-cycled in sitting position (SP) and at the other time in lying position (LP) when the participant was lying on her/his back. Cycling cadence was 60 revolutions per minute. A metronome guided the participant to keep this cadence. Cycling was performed in 6 conditions in both body positions: cycling bimanually and cycling by only one of the arms (left/right) and the radius of the circle in which the hand moved was either 15 or 20 cm. Thus the left arm cycled in 4 conditions and the right arm cycled also in 4 out of the 6 conditions both in LP and SP. The order of cycling conditions was randomly chosen. In each condition the participant cycled for 30 seconds and there was 30s pause between cycling in different conditions. Muscle activities (surface EMGs) were recorded from the biceps, triceps, delta anterior and delta posterior muscles in both arms. The movements were represented in the 4 dimensional ,,muscle space" of each arm and variances of filtered, smoothed EMG activities across cycles were computed. Variances obtained in SP and LP were compared by t test ($p<0.05$) in each cycling condition separately. There was significant effect of body position on muscle activity variances in the left arm: muscle activity variances in any condition were higher when cycling was performed in SP compared to variances obtained in LP and this difference was significant in all cycling condition (bimanual, unimanual, moving the hand on circles with radius of 15 and 20 cm). Considering the right arm, the body position did not have a significant effect on muscle activity variances in any cycling condition. Interestingly, in sitting position muscle activity variances in the non-dominant arm were higher and in laying position they were smaller compared to the dominant arm. We conclude that muscle activity adjustments to altered body position differ in the two arms. The motor control of the non-dominant arm is unstable when arm cycling is performed in SP compared to cycling in LP. This should be considered in medical rehabilitation and training protocols. Arm cycling trainings are proposed to be performed in lying position, because in this case muscle activity patterns in the non-dominant arm are less variable than in sitting position and the stability of muscle activities in the dominant arm is equally strong in the two body positions.

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Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.03/JJ10

Topic: E.04. Voluntary Movements

Title: Anodal transcranial direct current stimulation impacts the underlying control processes in bimanual movements

Authors: A. MCCULLOCH[1], I. PARK[1], J. CHEN[1], T. KIM[1], H. KIM[1], M. NAZIFI[1], D. L. WRIGHT[2], *J. J. BUCHANAN[3]
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Abstract: Participants produced rhythmic bimanual movement patterns using the index fingers. Two patterns were performed: in-phase, homologous flexion and extension between fingers; and anti-phase, alternating flexion and extension between fingers. Participants performed these tasks while maintaining cycle pace with a systematically increasing auditory metronome. Overall, anti-phase is a less stable movement pattern than in-phase at higher frequencies. As frequency increases, a spontaneous transition occurs from anti-phase to in-phase. A recent study using transcranial direct current stimulation (tDCS) reported a delay in the onset (time-to-transition, TTT) of the transition from anti-phase to in-phase (Carter, Maslovaat, & Carlsen, 2015). We modulated the excitability of the supplementary motor area (SMA) and the right primary motor cortex (M1) in an attempt to delay anti-phase TTT. Participants completed one session without stimulation and two session where they received anodal tDCS. Movement data collected in session one, without stimulation, served as a baseline measure. In session two and three, participants received offline anodal tDCS to either the SMA or right M1 prior to the movement tasks. Our data showed that TTT was longer in the SMA condition compared to baseline but it did not reach significance. However, tDCS of M1 resulted in a significantly longer TTT compared to both the baseline and SMA conditions. Mean relative phase showed the anti-phase pattern maintained coordination at higher frequencies after M1 stimulation whereas in-phase showed no change. In addition, the anti-phase pattern after M1 stimulation had a lower root mean square error at higher frequencies when compared to anti-phase after SMA stimulation and during baseline trials. When compared to baseline trials, task performance after M1 stimulation revealed the amplitude for the left finger, the stimulation target, was maintained while right finger amplitude decreased. For in-phase movements after both SMA and M1 stimulation, the right finger amplitude was reduced across all frequency plateaus compared to baseline. The current findings revealed that an increase in M1 excitability delayed the TTT from anti-phase to in-phase in a manner similar to previous work that stimulated SMA. While not significant, the delay in TTT following SMA stimulation compared to baseline was in the anticipated direction.

The findings may also indicate an effect of tDCS on movement amplitude for left and right fingers during in-phase and anti-phase.

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Poster

152. Motor Coordination and Bimanual Control

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Topic: E.04. Voluntary Movements

Support: NSF Award EEC-1028725

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Title: Interhemispheric interactions modulate behavioral responses during a reaction time task in non-human primates

Authors: *R. YUN[1], A. R. BOGAARD[2], A. G. RICHARDSON[4], S. ZANOS[5], E. E. FETZ[3]
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Abstract: Past studies applied electrical cortical stimulation (ECS) to test interhemispheric signaling and found that ECS had significant suppressive effects on the contralateral cortex, suggesting the recruitment of inhibitory transcallosal pathways. These results, deemed interhemispheric inhibition (IHI) and the ipsilateral silent period, suggest an intriguing role for inhibition in interhemispheric signaling, but it isn't clear whether such interactions occur during natural movements. We sought to document the functional and behavioral consequences of manipulating the IHI in a reaction time (RT) task, and to test whether effective connectivity between hemispheres changed with ECS using intracortical recordings. Three macaca nemestrina monkeys (I,K,U) were trained in an asynchronous bimanual wrist extension task and implanted with an electrode array (I: ECoG; K,U: bipolar intracortical) over sensorimotor cortex bilaterally for recording local field potentials (LFP) and for delivering ECS. Accelerometers were temporarily fitted to the dorsum of each hand and used to control two separate cursors. During a given trial, the monkey was randomly cued to move only the left or right cursor by rapidly extending the corresponding wrist. Experiments consisted, in order, of a preconditioning period (PRE, 500 trials), conditioning period (COND, 1000 trials), and a postconditioning period (POST, 500 trials). Suprathreshold ECS was delivered between electrodes that elicited a twitch

registered by the contralateral accelerometer (10 pulses, 0.2ms width, 333Hz; U,K: ~200uA; I: ~1mA). ECS was delivered to one hemisphere during either ipsilateral (IPSI) or contralateral (CONTRA) trials during the COND epoch. All monkeys performed the task regularly (280±14.3 ms mean RT), which allowed for CS to be timed relative to volitional cortical activation, indicated by readiness potential (RP). During contra experiments, ECS delivered before RP shortened the contralateral RT (CRT) and slowed the ipsilateral RT (IRT). On the other hand, CS delivered after RP had the opposite effect: CRT slowed and IRT sped up. Latencies during IPSI experiments demonstrated the same positive correlation with CRT, but were also positively correlated with IRT. Controls without stimulation, and with randomly timed stimulation, did not produce any significant effects. Many of these changes persisted during trials without stimulation, suggesting that plasticity may be involved. Overall, these results suggest that ECS can change the functional coupling between hemispheres when delivered at different times relative to the RP, and further analysis using the LFP will test these findings.

Disclosures: R. Yun: None. **A.R. Bogaard:** None. **A.G. Richardson:** None. **S. Zanos:** None. **E.E. Fetz:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.05/JJ12

Topic: E.04. Voluntary Movements

Support: NIH 5R01HD065438

Title: Bimanual use in chronic stroke survivors with left or right hemiparesis is differentially influenced by ipsilesional arm function

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Abstract: Background
It is well known by now that a unilateral CVA renders an individual with significant motor deficits of not only the side contralateral to the stroke lesion, but also on the side ipsilateral to it. In the performance of bimanual tasks, both arms play important functional roles in achieving the task goal. Despite growing evidence pertaining to arm use after stroke, little is known about how stroke survivors solve ecologically relevant bimanual tasks and what is the relative effect of the motor functional ability of the two arms on use patterns adopted for such tasks. The purpose of this study, therefore, was two-fold: 1) to identify volitional arm use patterns adopted for symmetric and asymmetric bimanual tasks and compare these patterns between left (LHP) and right-hemiparetic (RHP) individuals, and, 2) to examine if the relative motor functional ability of

the paretic and non-paretic arms could predict use patterns adopted for bimanual tasks.

Methods

To identify arm use patterns, we conducted a retrospective classification analysis of video data from two bimanual tasks performed as part of the Actual Amount of Use Test. Arm use patterns of 50 pre-morbidly right-handed stroke survivors were classified, first by the number of hands used (i.e. unimanual or bimanual), and second by the role in which the paretic arm was engaged (i.e. stabilization or manipulation). Logistic regression was used to analyze the effect of impairment level, side of affection, and task demands on the observed use patterns. Next, to examine the influence of motor functional ability on the observed use patterns, Wolf Motor Function test (WMFT) scores of the paretic and non-paretic arms were log transformed and used to predict arm use patterns. Correlation and discriminability statistics were used to determine group differences.

Results

There was a significant difference between LHP and RHP groups averaged across motor impairment (Upper-Extremity Fugl-Meyer: 19-66). Probability of bimanual-engagement was higher for the RHP compared to the LHP group, and this difference was greater for those with moderate-to-severe impairment. Motor functional deficits assessed by the WMFT of non-paretic arm were strongly positively correlated to functional deficits of the paretic arm, only in individuals with right hemiparesis (RHP), and not those with left hemiparesis (LHP).

Conclusions

Functional ability of the paretic and non-paretic arms seems to be ‘decoupled’ in individuals with LHP (non-dominant paresis), but not RHP (dominant paresis). This discrepancy in function between the two arms also predicts differences between LHP and RHP groups observed in arm use patterns adopted for bimanual tasks.

Disclosures: **R. Varghese:** None. **C. Winstein:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.06/JJ13

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI 17k17724 (ST)

JSPS KAKENHI 26120008 (ST)

“BMI Development” of SRPBS-AMED (ST & HI)

JSPS KAKENHI 26120002 (HI)

ImPACT (HI)

Title: Experimental evaluation of voluntarily activatable muscle synergies

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Abstract: Muscle synergy hypothesis implicitly assumed that individual muscle synergies are neurophysiologically independent of each other and voluntarily controllable. However, this assumption has not been empirically tested. This study tested if human subjects can voluntarily activate the individual muscle synergies extracted by non-negative matrix factorization (NMF), which is the standard mathematical method for the muscle synergy extraction. Ten healthy subjects performed isometric force production task with their right hand, and their 13 muscle activity patterns associated with the elbow and shoulder movements were measured. We extracted muscle synergies during the task by using the EMG data and NMF method. We also extracted the muscle synergies with different sparsity by using the NMF with the different number of muscle synergies. We defined a conventional muscle synergy as the muscle synergy extracted by the conventionally used index of reconstruction, i.e., the variability accounted for (VAF) and the coefficient of determination (CD), and by the index one more than VAF or CD. To test a validity of conventional method, we also defined an extended muscle synergy as the muscle synergy extracted by the number of muscle synergies that is more than that of the conventional muscle synergy. To examine whether the individual muscle synergy is voluntarily activatable or not, we calculated the index of independent activation which reflects a similarity between one muscle synergy and current muscle activation pattern of subject. Subjects were visually feed backed the index of independent activation, and tried to voluntarily activate the individual muscle synergy. The index of independent activation was statistically evaluated (α = 0.025). As a result, average of 90.8% of the muscle synergy extracted by the VAF was significantly activated. However, a rate of activatable muscle synergies of the other conventional muscle synergies was lower. Moreover, average of 25.5% of the extended muscle synergy was significantly activatable. Therefore, our results partly support the hypothesis, and indicate that the conventional method can estimate voluntarily activatable muscle synergies by using appropriate index of reconstruction. Moreover, it is suggested that the CNS can use sparser muscle synergies to perform voluntary movements.

Disclosures: S. Togo: None. **H. Imamizu:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.07/JJ14

Topic: E.04. Voluntary Movements

Title: Dynamic and static position sense of body targets in three dimensions

Authors: *C. R. COFFMAN[1], F. R. NAJDAWI[1], W. G. DARLING[2]
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Abstract: Much research on proprioception has been focused on the ability to match angles at joints such as the elbow, ankle, or knee in perceptual tasks (e.g., Goble et al 2012, Phys Ther 90:1176), or has been constrained to two dimensional tasks. Our recent work (Coffman et al., in preparation) showed greater accuracy when reaching with the right arm to appose the right index-tip to the moving than to the static left index-tip without vision. We aimed to investigate proprioceptive acuity for various locations on the body to test for differences according to target location. We hypothesized that reaching to touch hand and head targets would be more accurate than for trunk and lower limb targets because of hand use in bimanual coordination and in bringing the hand toward the head. We recruited 8 young adults (3 males), and placed motion sensors on the right index tip, head (nose, left earlobe, jugular notch), left hand (thumb tip, 4^{th} digit tip, 5^{th} digit tip), left arm (elbow), left leg (knee) and left foot (hallux tip, 4^{th} digit tip) to serve as proprioceptive targets. Participants were told to reach to touch the instructed target with the right index-tip in a single smooth movement under 3 conditions - Vision Static (VS - point to a static target) and No Vision (NVS - point to a static target without vision, NVD - point to a moving target without vision). Mean errors without vision (3D distance between the sensor on the nail of the index and the target) were very low for head and hand digit targets (average of 1.64 cm) but higher ($p < 0.001$) for trunk and lower limb targets (average of 2.98 cm). Variable distance errors were also lower for hand digit and axial targets ($p < 0.01$). Accuracy was similar for moving and static targets. Notably, errors at each target were much smaller than what might be expected from joint angle matching studies. Imposing movement of a body segment did not cause larger errors in locating targets on that segment. Differences in target localization for different regions of the body may reflect differences in available sensory input (e.g. the vestibular system for head targets) and differences in common use of certain targets (e.g. reaches to the other hand and to the mouth/nose and ear are more common than reaches to elbow and lower limb).

Disclosures: C.R. Coffman: None. **F.R. Najdawi:** None. **W.G. Darling:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

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Program#/Poster#: 152.08/JJ15

Topic: E.04. Voluntary Movements

Title: Age minimally affects proprioception of index finger location and motion

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Abstract: Loss of cutaneous receptors and muscle spindles with age have been demonstrated and may reduce proprioceptive acuity. However, proprioceptive acuity at the elbow assessed with perceptual reports was reduced by only 2^o-4^o in older subjects (Adamo et al. 2007 Percept Mot Skills 104:1297). Others have reported no effects of aging on proprioception for locating an unseen finger or touching facial features (Lovelace and Aikens 1990 Percept Mot Skills 70:1131). Because knowledge of fingertip location is important for many precise bimanual motor tasks, we examined effects of aging on accuracy of reaching with the right index tip to touch the left index tip in various locations in 3D space under static and dynamic conditions. We compared performance of 13 community dwelling older adults (73 +/- 5.1 years) with that of 14 younger adults (20 +/- 1.4 years) in 1 task with vision allowed (Vision Dynamic Active or VDA in which subjects actively reached with the right upper limb to touch the right index tip to the actively moved left index tip) and 4 tasks with vision blocked; NVDA – same as VDA but vision blocked; NVDP – same as NVDA but with passive motion of the left arm by the experimenter; NVSA – same as NVDA except left upper limb actively moved and held in position by the subject; NVSP – same as NVSA except the experimenter passively moved and held the left upper limb). Both young and older subjects perform these tasks with remarkable accuracy (mean 3D distance errors between sensors on the finger nails under 2.5 cm) with better acuity in dynamic than in static conditions by 1.23 cm ($p<0.001$). Indeed, performance in the dynamic tasks with vision allowed averaged only 0.3 cm better than while blindfolded. Older subjects mean 3D distance errors averaged only 0.2 cm larger in dynamic tasks ($p = 0.02$) and only 0.6 cm larger in static tasks than young subjects ($p = 0.07$) and differed by only 1-2 mm between active and passive conditions. Variable distance errors did not differ between young and older subjects in static or dynamic tasks ($p=0.35$). Overall, these data clearly show that elderly subjects have at most only slight decrements in proprioceptive awareness of fingertip location under static and dynamic conditions. Moreover, minimal differences in performance under active and passive condition cast doubt on contributions of internal models to proprioception.

Disclosures: W.G. Darling: None. **C.R. Coffman:** None. **C. Capaday:** None.

Poster

152. Motor Coordination and Bimanual Control

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.09/JJ16

Topic: E.04. Voluntary Movements

Support: ACSM Foundation Doctoral Student Research Grant

Title: Age-related changes in interlimb coordination of complementary bilateral arm movements

Authors: *E. J. WOYTOWICZ[1], K. P. WESTLAKE[1], R. L. SAINBURG[2], J. WHITALL[1]
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Abstract: We previously demonstrated that lateralization of neural control of predictive and impedance mechanisms are reflected by interlimb differences in control of bilateral tasks. Aging has been shown to reduce lateralization of both cognitive (Cabeza, 2002) and motor (Fling & Seidler, 2012) tasks, although the effect of aging on motor lateralization is controversial. We now ask whether aging affects bilateral coordination during mechanically coupled tasks that require one arm to stabilize while the other reaches toward targets. Right arm dominant young and older adults performed a bilateral task within a virtual reality system (Kinereach), in which the arms were connected by a spring. In a modified center-out task, one hand was required to impede the spring load to maintain its position at the origin of the task and the other moved to a series of targets distributed across a range of directions. During condition one, the right hand reached while the left hand stabilized, and during condition two, the left hand reached while the right hand stabilized. The order of the conditions was counterbalanced between subjects in both groups. The Test of Everyday Attention was used to assess cognitive function. Preliminary results (young, N=20; old, N=10) indicated that right arm reaching performance was more linear than left arm movements in both young and older adults. In contrast, the left arm stabilized against the spring forces better than the right, showing less displacement and lower endpoint compliance. In terms of age-related differences, the older adults demonstrated greater stabilizing deficits of the right hand than the younger adults. Further, greater stabilizing asymmetry was related to reduced visual attention in older adults. These findings suggest a) specialization of the right (dominant) arm for predictive control during bilateral complementary tasks is preserved with aging; b) deficits in dominant right-arm impedance control are greater in older than younger adults, indicating an increase rather than a decrease in this aspect of motor lateralization; and c) Age related deficits in dominant arm impedance control were associated with reduced attention in older adults. To date, this is the first demonstration of greater upper extremity lateralization with aging within the context of a bilateral complementary task. Future investigations building

on these results have the potential to ameliorate cognitive and motor decline in older adults and develop rehabilitation approaches for older adults with neurological disorders, such as stroke.

Disclosures: E.J. Woytowicz: None. **K.P. Westlake:** None. **R.L. Sainburg:** None. **J. Whitall:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.10/JJ17

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Emergent synergistic grasp behaviour in a visuomotor joint action task: Evidence for internal forward models as building blocks of human social interactions

Authors: *L. GUO, M. NIEMEIER
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Abstract: Central to the mechanistic understanding of the human mind is to clarify how high level cognitions arise from simpler sensory and motor functions. A longstanding assumption is that forward models used by sensorimotor control to anticipate actions also serve to incorporate other people's actions and intentions, and give rise to core aspects of human social cognitions. To test whether forward models can be deliberately used to coordinate social interactions, here we measured the movements of pairs of participants in a novel joint action task. For the task they collaborated to lift an object, each of them using fingers of one hand to push against the object from opposite sides, just like a single person would use two hands to grasp the object bimanually. Perturbations of the object were applied randomly as they are known to impact grasp-specific movement components in common grasping tasks. We found that co-actors quickly learned to make grasp-like movements with grasp components that were coordinated offline based on action observation of peak deviation and velocity of their partner's trajectories. Our data suggest that co-actors adopted pre-existing bimanual grasp programs for their own body to use forward models of their partner's effectors. This confirms the idea that human cognitions have deliberate access to sensorimotor forward models to plan social behaviour.

Disclosures: L. Guo: None. **M. Niemeier:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.11/JJ18

Topic: E.04. Voluntary Movements

Title: Stability of bimanual finger coordination is constrained by salient phase

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Abstract: Rhythmic bimanual two-finger tapping movements have a tendency for symmetrical patterns to dominate over asymmetrical ones when both hands are pronated. When one hand is supinated, the asymmetrical pattern becomes dominant over the symmetrical pattern. This is unexpected, since many types of bimanual coordination are stable in the symmetrical pattern irrespective of posture. It is still unclear why bimanual two-finger tapping is an exception. In this study we examined whether the relative-salience hypothesis could explain this exception. The relative-salience hypothesis proposes that two cyclic joint movements tend to be conceived as a stream of a unified event, and if a point in the unified event is perceptually conceived of as the most salient sub-event, the sequences of the most salient sub-events will have a tendency to go together in concurrent two event streams. In experiment 1, the difference in salience between unimanual two-finger tapping under different combinations of fingers was evaluated by assessing the stability of sensorimotor coordination. Subjects performed unimanual two-finger tapping, following the beat of an auditory metronome. Finger combinations of index and middle fingers, and middle and ring fingers were used with two modes of coordination (e.g., index finger tapping on the beat with middle finger tapping off the beat, and the index finger tapping off the beat with the middle finger tapping on the beat). Index finger tapping on the beat was more stable than middle finger tapping on the beat. Also, middle finger tapping on the beat was more stable than ring finger tapping on the beat. Thus the extent of salience in finger tapping in the order of highest to lowest is index, middle, and ring fingers. In experiment 2, subjects performed four kinds of bimanual two-finger tapping at 2 Hz without external pacing signals in the following finger combinations: 1) index and middle fingers of both hands, 2) middle and ring fingers of both hands, 3) left ring and middle fingers and right index and middle fingers, and 4) left middle and index fingers and right middle and ring fingers. Subjects performed two modes of coordination (symmetry and asymmetry) with either a pronated or a supinated right forearm. Under all conditions, the more stable pattern occurred when timing of the more salient tapping for each hand was simultaneous compared to that which was alternate. This effect was independent of direction in external space or contraction timing of the homologous muscles.

Accordingly, the stability of bimanual two-finger tapping was constrained by timing of the salient point for each hand.

Disclosures: Y. Zheng: None. **T. Muraoka:** None. **K. Kanosue:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

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Program#/Poster#: 152.12/JJ19

Topic: E.04. Voluntary Movements

Title: Interactions between hands after force field perturbation of one hand

Authors: *P. C. DESROCHERS[1], A. T. BRUNFELDT[2], F. A. KAGERER[1]
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Abstract: Bimanual movements are common in daily life and require a high degree of coordination. Incongruous bimanual movements can cause interference between the hands as each hand attempts to perform independent action. Interference is thought to result from sharing of information between the hemispheres. While interference has been observed as a result of a visuomotor perturbation, it is unknown whether a kinetic perturbation results in similar levels of interference, and if so, whether the perturbation differentially affects feedforward or feedback processes. Twenty-one participants, randomly assigned to three groups, moved two robotic manipulanda simultaneously from two home positions to two target positions located 10 cm forward or backward of the home positions. Hand position was represented by a cursor on a screen that occluded the view of the hands. Participants performed reaches during two blocks of 10 trials without perturbation. In block 1, hand feedback was displayed for both hands; in block 2, visual feedback of the left hand was removed, requiring participants to rely on kinesthetic control for that hand. In the exposure block of 140 trials, participants were exposed to a kinetic perturbation consisting of a velocity-dependent lateral force during reaches away from the body, and a medial force during reaches towards the body. One group received a force field of 25 N per m/s, a second group a force field of 15 N per m/s, and a third group received no perturbation. Both perturbed groups were instructed to continue moving the invisible left hand straight to the targets during the right hand perturbation. In the final block of 40 trials, no force was applied to the right hand for all groups. Results showed that the perturbed groups adapted to the perturbation of the right hand, both with substantial aftereffects in the final block. In the perturbed groups, the left, invisible hand deviated from its straight path due to interference from the perturbed right hand. Additionally, preliminary analyses showed that the left hand performance differed minimally between the two perturbed groups, with greater interference in the 25 N per m/s group. Finally, a majority of participants adopted an anisodirectional pattern of interference, as opposed to the isodirectional pattern predominantly found in visuomotor

interference paradigms. The data demonstrate that a kinetic perturbation in the right hand affects straight reaching trajectories in the left hand. Furthermore, comparisons between studies showing interference as a result of visuomotor perturbations of one hand will allow us to determine if the information shared between hemispheres differs between tasks.

Disclosures: P.C. Desrochers: None. **A.T. Brunfeldt:** None. **F.A. Kagerer:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.13/JJ20

Topic: E.04. Voluntary Movements

Support: Michigan State University Distinguished Fellowship

Michigan State University Summer Renewable Research Fellowship

Title: Bimanual task dynamics affect spatial but not temporal movement characteristics

Authors: *A. T. BRUNFELDT[1], P. C. DESROCHERS[2], F. A. KAGERER[2]
[2]Dept. of Kinesiology, [1]Michigan State Univ., East Lansing, MI

Abstract: Previous studies have shown that interference in dynamical and isometric bimanual tasks increases as the force demands also increase. For center-out movement tasks in which visual feedback for one hand is perturbed while the other hand operates without visual feedback, we have shown spatial interference in the control of the invisible hand. The purpose of this study was to determine the effect of task kinetics on spatial interference during a discrete bimanual task. Our hypothesis was that as force required to move the upper limbs increased, spatial interference would increase. Related to this, we investigated the effect of task kinetics on temporal coupling between the hands. Right-handed participants (n=45) performed a bimanual center-out reaching task using a KINARM endpoint robot to two peripheral targets either 90^{o} or 270^{o} (distance 10cm). Participants were provided visual feedback of hand position with two cursors, but vision of the hands was occluded. Following a visual baseline with veridical visual feedback, the cursor display of the left hand was removed, and participants were instructed to move to where they thought they would hit the target. The exposure phase consisted of 140 trials with a 40^{o} visual feedback rotation for the right hand. Throughout the task, we modulated task kinetics by applying a restoring force at the manipulanda handles directed toward home positions. Participants were randomly assigned to one of three groups: 0-, 30-, or 60-N/m. Spatial interference was assessed using initial directional error (IDE) and lateral endpoint error (EPX). A force channel in the left hand in 20% of trials allowed us to determine the lateral force resulting from interference. IDE results showed all three groups adapted similarly with their right hand to

the perturbation. Both IDE and EPX in the invisible left hand increased over time, with the 30N/m and 60N/m groups showing greater interference compared to the 0N/m group. The effect was greater for EPX than IDE. For the error clamp trials, we found a dose-response increase in lateral force, which monotonically increased with reach displacement. For temporal coordination, the right hand started and ended movement before the left during baseline; during exposure, the left hand started and ended movement before the right. Overall, these results support the prediction that increased force production in both hands results in increased interference in the invisible hand. Additionally, task kinetics influence feedback-related processes (reflected by EPX and lateral force) more so than feedforward processes (IDE). Finally, task kinetics influence spatial, rather than temporal characteristics of movement.

Disclosures: A.T. Brunfeldt: None. **P.C. Desrochers:** None. **F.A. Kagerer:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

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Program#/Poster#: 152.14/JJ21

Topic: E.04. Voluntary Movements

Title: Interlimb differences in wrist diadochokinesis

Authors: *G. A. SRINIVASAN, R. SAINBURG
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Abstract: Previous research from our laboratory has led to a model of motor lateralization in which each hemisphere contributes specialized control mechanisms to both arms. We proposed that the hemisphere contralateral to the dominant arm is specialized for predicting the effects of limb dynamics, such as interaction torques. However, this hypothesis has thus far only been tested in complex tasks that required substantial visuomotor and cognitive processing, complicating our interpretation of results. Our hypothesis predicts substantial asymmetry in even simple tasks that do not require visual feedback nor substantial cognitive monitoring, but that do require precise biomechanical control. Radial-ulnar deviation of the wrist requires precise coordination between the carpi muscles, which have substantial moment arms across all 3 axes of wrist motion. As a result, precise coordination among muscle activations is required to prevent motion along uninstructed degrees of freedom. In addition, angular displacement in one degree of freedom affects the moment arm across other degrees of freedom. We predict that rapid alternating radial-ulnar deviation should elicit substantial motion along non-instructed degrees of freedom (flexion-extension and pronation-supination) in the non-dominant, but not in the dominant arm. In our task, we physically constrain pronation-supination angle, limiting the task to radial-ulnar deviation and flexion-extension. We also predict that rapid alternating flexion-extension of the wrist will not show interlimb differences in the uninstructed degree of freedom

(wrist deviation) due to extrinsic muscles that do not have substantial radial-ulnar deviation moment arms. We quantify this coordination as maximum non-instructed angular excursion during a cycle of motion, normalized to maximum angular excursion in the instructed degree of freedom. Furthermore, because we hypothesize that such coordination is the defining characteristic of handedness, we predict a substantial correlation between the interlimb differences of our measure of wrist coordination and the Edinburgh Handedness Inventory, the current accepted measure of hand-preference. Our preliminary results support these predictions: Interlimb differences in normalized excursion were substantial for radial-ulnar deviation, but insignificant for flexion-extension movements. Correlations with handedness are pending further results.

Disclosures: G.A. Srinivasan: None. **R. Sainburg:** None.

Poster

152. Motor Coordination and Bimanual Control

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Topic: E.04. Voluntary Movements

Support: NSF Grant BCS-1153034

NSF Grant BCS-1152916

Title: Hand position and forces covary during anticipatory control of bimanual manipulation

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Abstract: Recent studies on anticipatory planning of object manipulation have investigated the interdependency of kinematics (hand shaping and digit position) and kinetics. Specifically, studies have shown that there is a strong covariation of digit position and load forces during the performance of a two-digit lift and whole-hand manipulation. This highlights the integration of such cortical areas of control in motor planning. The generalizability of this behavior to bimanual manipulation has yet to be established. A main difference between two-digit precision grasping and whole hand manipulation is that in whole hand manipulation, modulation of digit position was driven predominantly by the thumb, as opposed to both the thumb and fingers. Thus, the physiology of the effectors affects the specifics of the behavior. We investigated the coordination of hand position and forces during a bimanual manipulation of an object with variable center of mass. Participants were instructed to prevent object roll during the lift. Similar to the other forms of grasping, we found a covariation of hand position and forces. This shows

the generalizability of effector position modulation as a function of effector force modulation. Because of the anatomical features of the hand, variations in hand position were offset by the larger contact surface. Thus, even though the grasping behavior is generalizable, different effectors are adapted based on their biomechanical constraints to perform the task. These results highlight the neural representation of objects and underscore a motor plan that can be implemented in a range of effectors resulting in a continuum of position and force modulation for object manipulation.

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Poster

152. Motor Coordination and Bimanual Control

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Title: Age-related declines in motor performance are associated with decreased segregation of large-scale brain networks

Authors: *B. R. KING[1], P. VAN RUITENBEEK[3,1], I. LEUNISSEN[1], K. CUYPERS[1], K.-F. HEISE[1], T. SANTOS MONTEIRO[1], L. HERMANS[1], O. LEVIN[1], G. ALBOUY[1], D. MANTINI[1,4,5], S. SWINNEN[1,2]
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Abstract: Aging is associated with substantial declines in motor functioning as well as robust changes in the functional organization (i.e., connectivity) of brain networks. Previous research has investigated the link between these two age-varying factors but examinations were predominantly limited to the functional organization *within* motor-related brain networks. Little is known about the relationship between age-related behavioral impairments and changes in functional organization at the whole brain (i.e., multiple network) level. This knowledge gap is surprising given that the decreased segregation of brain networks (i.e., increased inter-network connectivity) can be considered a hallmark of the aging process. To fill this gap, we investigated the association between declines in motor performance across the adult lifespan and the

functional connectivity within and between both motor and non-motor resting state networks. Ninety-six participants between 20 and 75 years of age completed a bimanual coordination task and a resting state fMRI scan in experimental sessions separated by approximately one week. Eighty-four seed regions from the 14 resting state networks identified in an independent sample of participants in previous research by our group were extracted. BOLD signal across all voxels within each seed were averaged and Pearson correlation coefficients among all seeds were converted to Z-values. To assess age- and motor performance-related modulations in resting state functional connectivity, single-subject correlations between seed pairs were correlated with the participants' age and performance on the bimanual coordination task. Results demonstrated that stronger *inter*-network resting state connectivity observed as a function of age was significantly related to worse motor performance. Moreover, bimanual coordination performance had a significantly stronger association with *inter*-network connectivity than *intra*-network connectivity, including connectivity within 2 motor networks. These findings suggest that age-related declines in motor performance may be attributed to a breakdown in the functional organization of large-scale brain networks rather than simply age-related connectivity changes within motor-related networks. It would be advantageous for future research to extend analyses beyond strictly motor networks, as connectivity *between* networks appears to have a significantly stronger association with motor behavior.

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Poster

152. Motor Coordination and Bimanual Control

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Topic: E.04. Voluntary Movements

Title: The effect of coordination complexity on reaction time is affected by age in a choice multi-limb reaction time task

Authors: *S. VERSTRAELEN[1], K. CUYPERS[1,2], R. L. J. MEESEN[1]
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Abstract: Introduction Healthy aging is known to be associated with deterioration of at least some motor functions, such as slowing of reaction times (RT). While previous research has mainly focused on age-related declines in RT by the use of simple uni- or bimanual RT paradigms, the effect of age on RT in more complex motor tasks is less investigated. The aim of the current study was to determine whether the effect of age on RT is dependent on coordination

complexity. **Methodology** 41 young adults (mean age, 19.7 years; range, 18-23 years; 21 females) and 35 older adults (mean age, 72.8 years; range, 64-84 years; 18 females) voluntary participated in the study. As RT is considered to be a measure for the speed of central processing, a choice multi-limb reaction time task (MUL-RT) is used to detect possible differences between groups. During this task, the participant is instructed to lift one, two, three or four limbs as quickly and accurately as possible, in accordance to what is indicated by the visual stimulus. **Results** Results revealed that the effect of coordination complexity on RT differs between age groups. Older adults showed a more pronounced increase in RT in the more complex conditions compared to less complex conditions than younger adults did. **Conclusion** These results suggest that the relationship between RT and coordination complexity in a choice MUL-RT task is affected by age. The current behavioural study might provide new insights for future studies, investigating how aging affects the neural interactions between the four limb presentations in the context of motor planning.

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Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Title: Bimanual reflexes during shared bimanual tasks are asymmetric

Authors: *J. SCHAFFER[1], R. L. SAINBURG[2]
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Abstract: Previous research has shown that during a bilateral task in which both arms carry a single virtual object, perturbation to the dominant arm produces reflexive responses in the non-dominant arm shoulder muscles. However, when the same bilateral motions are performed without a common object, bilateral reflex responses are absent (Mutha and Sainburg, 2009). These findings indicate task dependent modulation of both short and long latency components of the stretch reflex, which is likely mediated by descending influences on spinal circuitry. Given substantial asymmetries in hemispheric control of arm movement, we now ask whether task-dependent bilateral reflexes are symmetric.
We tested this question using a virtual object manipulation task. In a virtual reality environment, a cursor representing each hand is used to ‘pick up’ each end of a bar and “drag” it to a target. At the onset of occasional and unpredictable trials, a solenoid engaged for 200 milliseconds, preventing motion along the antero-posterior axis for one of the arms. This prevented ongoing extension of the elbow and resulted in acceleration of the shoulder into horizontal adduction.

Thus, the effect of the perturbation was to 'stretch' the shortening triceps brachii, as well as the lengthening posterior deltoid (relative to baseline movements). We binned muscle activity into 2 intervals, relative to the initiation of the perturbation: 1) short latency (20-45 ms) and 2) long latency (46-75 ms). We compared muscle activity in these two bins to the corresponding activity in non-perturbed trials. This comparison was done for both the ipsilateral perturbed arm and in the contralateral unperturbed arm.
Unilateral responses in the ipsilateral arm: Regardless of which arm was perturbed, ipsilateral responses were similar: Short latency responses were significant in the posterior deltoid, while long latency responses were significant in the triceps brachii. However short latency responses in triceps only reached significance in the dominant (right) arm. **Bilateral responses in the contralateral arm:** The non-dominant posterior deltoid showed significant short and long latency reflex responses. However, for the dominant arm, short and long latency intervals were not significantly different from that of non-perturbed trials. Thus, bilateral reflex responses to unilateral perturbations are asymmetric, such that the non-dominant arm responds to perturbations of the dominant arm, but not vice versa.
Mutha PK, Sainburg RL. Shared bimanual tasks elicit bimanual reflexes during movement. J Neurophys. 2009;102(6):3142-3155.

Disclosures: J. Schaffer: None. **R.L. Sainburg:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.19/JJ26

Topic: E.04. Voluntary Movements

Title: Control of paretic and non-paretic arm during bimanual reaching movements after stroke

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Abstract: Eighty five percent of stroke survivors experience weakness of one upper extremity, which limits their ability to perform daily tasks. Bilateral arm training with rhythmic auditory cueing is one of the rehabilitation interventions, which includes the use of the non-paretic arm to facilitate the movement of the paretic arm. Specifically, the non-paretic arm allows the two arms to work as a single functional unit to promote the coordination and movement of the paretic arm. We previously studied joint control in the paretic arm during a reach-to-grasp movement. The findings suggested that these individuals have limited ability to anticipate and control for interaction torque during motion towards the target, and therefore, they tend to suppress interaction torque by muscle torque instead of exploiting the interaction torque for joint rotation. Here we investigated how the participation of the non-paretic arm influences joint control in both

arms during a single session when individuals with stroke perform bimanual reaching, with both arms reaching and grasping two exact same objects simultaneously. Participants reached for a soda can with their non-paretic arm (unimanual condition) and two soda cans simultaneously with the paretic and non-paretic hand simultaneously (bimanual condition). We compared the kinematic and joint control (torque) characteristics between the paretic arm in the unimanual and bimanual conditions. The paretic shoulder and elbow showed significantly greater ranges of motion in the bimanual condition than the unimanual condition. However, the movements were not faster and no improvements in the joint control were found. In particular, the degree of interaction torque suppression was not reduced. Surprisingly, the bimanual condition resulted in substantial deterioration of movements of the non-paretic arm. In addition to increased movement time, the non-paretic arm demonstrated increased levels of suppression of interaction torque at the shoulder and elbow. These results show that although bimanual movement performance improves the range of motion in the paretic arm, joint control underlying the translation of the hand toward the target is more resistant to the coupling between the two arms. Rather, this coupling results in deterioration of non-paretic arm movements.

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Poster

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Title: Differences in the internal representation of the two arms could explain hand dominance

Authors: *D. CORDOVA BULENS, F. CREVECOEUR, P. LEFEVRE
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Abstract: The dominant and non-dominant arms display differences when learning to reach in a force field consistent with predictive or impedance-based control. Because the intrinsic mechanical impedance of the limb is low (Crevecoeur and Scott, 2014, PLoS Comput Biol 10:e1003869), we suspect that these differences are in fact due to distinct control strategies. We suggest that the non-dominant arm uses a control strategy that is more robust but less flexible, while the dominant arm displays higher sensitivity to model error but is more adaptive.To address this question, we instructed participants (N=28) to perform reaching movements to a

visual target in the presence of a curl force field. Participants received only visual feedback of their end-point position. Three different targets were used, positioned 15 cm away from the starting position, in 60, 90 and 120° direction respectively. Targets were presented randomly and participants performed 80 trials per target. Participants were divided in two groups: one group performed the task with the non dominant arm first, and the other group with the dominant arm. We compared the results of two different groups of right-handed participants, one who performed the task (240 trials) first with their dominant hand and the other who performed the task first with their non-dominant hand. We extracted the average error and the end-point dispersion of the participants' movement for each moving window of 10 trials. We found that the average error and end-point dispersion were significantly smaller during the initial trials for participants who performed the task with the non-dominant arm ($p<0.05$). We further extracted the maximum deviation of the movement from the straight line linking the starting point and the target and found that the maximum deviation of the 5 first trials of the non-dominant arm movement was significantly smaller than for the dominant arm movements (T-test, $p<0.05$). We fitted a standard exponential learning curve of the form: $y=\beta0+\beta1*\exp(-\beta2\ x)$ on the maximal deviation of the movements of participants (x = trial number). We found that the learning rate ($\beta2$) for the non-dominant arm was significantly smaller than for the dominant arm ($p<0.05$), suggesting that the dominant arm learned faster. Despite the fact that the non-dominant arm appears to learn slower across trials, it is also more accurate and precise, and deviates less from the straight line during the initial trials which is consistent with a difference in the robustness of control strategy. We suggest that the different control strategies expressed by the dominant and non-dominant arms reflect differences in the internal representation across arms.

Disclosures: D. Cordova Bulens: None. **F. Crevecoeur:** None. **P. Lefevre:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.21/JJ28

Topic: E.04. Voluntary Movements

Title: The effects of neural crosstalk on interpersonal and intrapersonal coordination dynamics

Authors: *D. M. KENNEDY[1], A. J. KOVACS[2], C. SHEA[1]
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Abstract: A recent experiment (Kennedy et al., 2015) indicated consistent distortions in one limb that could be attributable to the production of force in the contralateral limb during a multi-frequency bimanual task. Although, neural crosstalk was implicated as a source for the observed distortions, it is also possible the distortions were due to incidental constraints associated with

the testing environment. Therefore, an experiment was designed to determine if similar distortions would be observed when two people (interpersonal coordination) were required to coordinate a pattern of force as when an individual (intrapersonal coordination) coordinated the same pattern. Participants (N=14, 7 pairs) were required to rhythmically coordinate a pattern of isometric forces in a 1:1 and 1:2 pattern of force using both limbs (intrapersonal control), their right limb coordinated with their partners left limb (interpersonal right), and their left limb coordinated with their partners right limb (interpersonal left). Given the lack of a neuromuscular linkage between paired partners in the interpersonal coordination conditions, it was predicted that distortions consistent with neural crosstalk would not be observed. Indeed, no such distortions in the force and force/velocity time series were observed in the interpersonal coordination conditions. However, the results indicated consistent distortions in the left limb that were coincident with the initiation of force in the right limb in the intrapersonal condition. These results support the notion that neural crosstalk may be responsible for the interference observed in complex intrapersonal bimanual tasks.

Disclosures: D.M. Kennedy: None. **A.J. Kovacs:** None. **C. Shea:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.22/JJ29

Topic: E.04. Voluntary Movements

Support: The Natural Sciences and Engineering Research Council of Canada

The Canadian Institutes of Health Research

Title: Specificity of sparing effects with cross-education in an immobilized limb

Authors: *J. W. ANDRUSHKO, J. L. LANOVAZ, K. M. BJÖRKMAN, S. A. KONTULAINEN, J. P. FARTHING
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Abstract: Cross-education (CE) is the phenomenon that occurs after unilateral strength training whereby strength of the untrained contralateral limb is enhanced. A handful of studies have shown that CE can spare the loss of strength and size of an opposite immobilized limb. While CE is known to show specificity to the homologous muscle, specificity has not been examined with an immobilization model and the mechanisms of the sparing effects are currently unclear. The effects may present differently with immobilization due to movement inhibition and altered corticospinal excitability. To investigate the specificity of CE sparing effects with immobilization sixteen participants were randomly assigned to a training (M=1, F=7; ht:

170.3±10.1 cm; wt: 77.2±19.2 kg) and control (M=2, F=6; ht: 169.3±8.5 cm; wt: 85.7±22.7 kg) group. Both groups wore a non-dominant forearm cast for 4 weeks. Two pre- and one post-testing session involved wrist flexors and extensors muscle thickness (ultrasound), eccentric (ECC), concentric (CON) and isometric (ISO), maximal voluntary contractions (dynamometer), electromyography (EMG) normalized to M_{max}, and forearm muscle cross-sectional area (MCSA; peripheral quantitative computed tomography). ECC wrist flexion was trained 3 times per week. Separate group × time interactions for the immobilized and non-immobilized limbs revealed that only the training group showed pooled strength preservation in the wrist flexors of the immobilized limb (Training: pre=12.3±5.4 Nm, post=12.0±4.6 Nm vs. Control: pre=14.8±5.4 Nm, post=11.6±4.6Nm; p=.04, η_p^2=.25) and increased wrist flexors strength of the non-immobilized limb (Training: pre=12.9±5.5 Nm, post=16.9±7.3 Nm vs Control: pre=14.9±5.5 Nm, post=13.8±7.3 Nm; p=.04, η_p^2=.27). Percent change in MCSA for the immobilized limb differed between training (1.4±1.5%) and control (-2.7±3.3%; p=.01, η_p^2=.43). Muscle thickness change differed between groups (Training; 2.7±4.4%, control; -3.2±3.2%) for the immobilized wrist flexors only (p=.01, η_p^2=.40). EMG data failed to reveal any significant between group or co-activation differences regardless of muscle (flexors, extensors), task (flexion, extension) or type (ECC, CON, ISO). Strength preservation was not specific to contraction type (p=.69, η_p^2=.03), yet sparing effects were specific only to the trained muscle. Although the mechanisms of muscle size preservation are currently unknown, these data draw a link between strength and size sparing with CE and suggest that ECC training of the non-immobilized limb can preserve size and strength of the immobilized contralateral homologous muscle across multiple contraction types.

Disclosures: **J.W. Andrushko:** None. **J.L. Lanovaz:** None. **K.M. Björkman:** None. **S.A. Kontulainen:** None. **J.P. Farthing:** None.

Poster

152. Motor Coordination and Bimanual Control

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Topic: E.04. Voluntary Movements

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Simon's Foundation

McKnight Scholar Award

Klingenstein-Simons Fellowship

Searle Scholars Program

Kavli Foundation

Title: Motor cortex activity during contralateral versus ipsilateral arm movements: Preserved response structure despite local reorganization of responses

Authors: *K. C. AMES, M. M. CHURCHLAND
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Abstract: The motor cortex of each hemisphere projects primarily to the contralateral side of the body, yet neurons can be active during ipsilateral arm movements. Such activity is consistent with a few possibilities. H1) The motor cortex may encode a high-level, effector independent representation of movement parameters. H2) The "driving cortex" may send signals to the other cortex, which become relevant when both arms must be coordinated. H3) While motor cortical output is lateralized, the overall computation may be shared between hemispheres.
We employed a task in which a monkey progresses through a virtual environment by cycling a right or left pedal with the corresponding hand. Simultaneous recordings (24-channel V-probes) yielded 178 and 190 left- and right-hemisphere units across days. Median firing-rate range was almost as high (86%) for ipsilateral versus contralateral movements. However, a neuron's activity pattern during driven arm movements only correlated weakly with its activity pattern during non-driven arm movements ($r = 0.15$). Furthermore, units that shared similar activity patterns during movements of one arm had little tendency to be similar during movements of the other arm ($r = 0.13$). Thus, while M1 is active during movements of either arm, at the individual-unit level there is a dramatic remapping of activity.
However, at the population level we found that all major signals present in the driving cortex were also present in the non-driving cortex. Arm muscle activity could be equally well-predicted by either the driving or non-driving cortex ($R^2 = 0.85$ and 0.83 respectively). Furthermore, activity of an individual unit could be predicted equally well by other units from the same or opposite hemisphere. Thus, even when only a single arm is moving, there are no strong patterns present in the driving cortex that are absent in the non-driving cortex.
Our results are inconsistent with an effector-independent representation (H1); the activity pattern of essentially all neurons was effector dependent. Our results do not exclude the possibility that the hemispheres act largely independently but send coordinating signals (H2). However, the coordinating signals would have to be quite complete, given the isomorphism of the population response between hemispheres. The logical extreme of that possibility is that the two hemispheres act as one large network despite anatomical segregation of outputs (H3). This hypothesis is consistent with the reorganization of responses; a common property of artificial recurrent networks is a reorganization of responses between tasks requiring very different outputs.

Disclosures: K.C. Ames: None. **M.M. Churchland:** None.

Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.24/KK1

Topic: E.04. Voluntary Movements

Title: Transcallosal inhibition elicited from non-primary motor areas in healthy individuals and chronic stroke

Authors: *J. L. NEVA[1], K. S. HAYWARD[2], K. E. BROWN[2], C. S. MANG[3], L. A. BOYD[2]
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Abstract: Interhemispheric inhibition (IHI) between primary motor cortices (M1) can be measured using single-pulse and dual-coil paired-pulse transcranial magnetic stimulation (TMSpp). TMSpp has been used to measure IHI between non-M1 regions, such as primary somatosensory (S1), dorsal premotor (PMd) and dorsolateral prefrontal (DLPFC) cortices, and M1 in young healthy individuals. However, IHI from non-M1 areas has not been tested using single-pulse TMS, nor has it been assessed in older adults or individuals with stroke. Here we quantify IHI by measuring transcallosal inhibition (TCI), via the ipsilateral silent period (iSP), applying TMS over distinct cortical regions as participants held an ipsilateral contraction. This study aimed to determine: 1) if an iSP is elicited with stimulation over non-M1 regions, 2) differences between iSP magnitude elicited from non-M1 regions in healthy individuals and chronic stroke, and 3) relationships between iSP elicited over each cortical area with function (Wolf Motor Function Test (WMFT)-rate) and impairment (Fugl-Meyer (FM)) in individuals with stroke.
Forty-two individuals participated: 9 young healthy (age=28±5), 13 older healthy (age=67±8), 10 mild-moderate impairment (FM >30/66), and 10 severe impairment (FM ≤30/66). TCI was measured with stimulation over M1, S1, PMd, DLPFC and superior parieto-occipital cortex (SPOC) bilaterally.
For healthy younger and older individuals, there was a significant decrease in muscle activity during the iSP compared to pre-stimulus muscle activity elicited over all cortical regions bilaterally ($p<.0002$). Further, the iSP magnitude was greater when elicited over M1 compared to DLPFC ($p=.013$), PMd ($p=.019$) and SPOC ($p=.0003$), with S1 demonstrating a similar iSP as M1. For individuals with chronic stroke, iSP magnitude in mild-moderate impairment showed greater iSP elicited over S1 compared to SPOC ($p=.02$). In contrast, SPOC showed greater iSP than DLPFC ($p=.03$), M1 ($p=.02$), and PMd ($p=.004$) with severe impairment. The iSP from contralesional M1 ($r=-0.49$, $p=.04$), PMd ($r=-0.53$, $p=.03$) and S1 ($r=-0.71$, $p=.001$) significantly correlated with FM, while contralesional DLPFC trended towards significance ($r=-0.44$, $p=.08$). iSP from contralesional S1 ($r=-0.57$, $p=.02$) and M1 ($r=-0.49$, $p=.05$) significantly correlated

with affected WMFT-rate.
Our results demonstrate two novel findings: 1) an iSP can be elicited with stimulation over non-M1 regions in healthy and chronic stroke individuals; and 2) iSP elicited from non-M1 regions reveals distinct neurophysiological communication between non-M1 regions and M1, which were related to impairment and function in chronic stroke.

Disclosures: **J.L. Neva:** None. **K.S. Hayward:** None. **K.E. Brown:** None. **C.S. Mang:** None. **L.A. Boyd:** None.

Poster

152. Motor Coordination and Bimanual Control

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Program#/Poster#: 152.25/KK2

Topic: E.04. Voluntary Movements

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JSPS KAKENHI 17K14933

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MEXT/AMED SRPBS (BMI)

JSPS KAKENHI 16K12476

Title: Dynamic modulation of brain activities during three-ball juggling

Authors: ***H. KAMBARA**[1], M. MIYAKOSHI[2], H. TANAKA[3], T. KAGAWA[4], N. YOSHIMURA[5], Y. KOIKE[6], S. MAKEIG[7]
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Abstract: This study reports an EEG experiment during juggling movements captured by simultaneous recording of body movements and high-density EEG signals, and dynamic modulations in both the time and frequency domains associated with juggling events. The origin of jugging goes back to ancient Egypt, Greek, and China, and the academic investigation of juggling has attracted traditionally mathematicians and robotics engineers, and most recently neuroscientists. Although successful performance of juggling requires different levels of manual

skills and eye-hand coordination that are not necessarily required in daily life, learning of basic juggling (e.g., three-ball cascade juggling) takes only hours to days. Recent MRI studies observed relatively rapid structural plasticity in cortical grey and white matters associated with juggling training on the time scale of weeks. However, fMRI constrains on body movements with low temporal resolution, so neural mechanisms of juggling skills on the sub-second order cannot be hitherto explored. EEG is only an option with high-temporal resolution but has not been frequently applied due to extensive movement-related artifacts. Here by exploiting recent advancements in measurement hardware and signal processing (collectively known as Mobile Brain/Body Imaging), we recorded EEG activities during juggling movements. Seven healthy amateur jugglers performed a three-ball cascade juggling task while their neural activities, body movements, and ball trajectories were monitored in synchrony with 205 EEG electrodes, a motion capture, and a video camera. The timings of catches and throws were defined, respectively, as the moments the ball contacted and left the hand which were determined by visually inspecting the frame images of video data. Independent component analysis extracted components associated with brain activities, followed by equivalent dipole fitting of those components localizing the corresponding cortical sources in the visual, somatosensory and motor cortical areas. We found that time courses of some ICs in the visual area were entrained with horizontal motions of the balls while others were entrained with vertical motions. ERPs of ICs in the sensorimotor areas were locked to the catching timings by the contralateral hands. Besides time courses, the powers of alpha and beta bands in visual ICs and the powers of alpha, beta and gamma in sensorimotor ICs were modulated dynamically in synchrony with juggling phases. This study, for the first time, demonstrates dynamic modulations of both temporal and frequency EEG features of the order of milliseconds synchronized with juggling events and phases.

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Poster

152. Motor Coordination and Bimanual Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 152.26/KK3

Topic: E.04. Voluntary Movements

Support: BK21 plus

Title: A behavioral model of bimanual motor coordination in mice

Authors: *M. JEONG, Y. KIM, D. KIM
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Abstract: Motor coordination of two hands or forelimbs is essential for animal behaviors. However, neural mechanisms underlying the execution of sequential bimanual movements are still largely unknown because it lacks behavioral models to observe in animal models such as rodent. Here, we developed a head-fixed bimanual press task that each press is performed by different forelimbs in mice. Water-deprived mice should press both left and right switches by left and right forelimbs, respectively in sequence, to get water rewards. We confirmed that success rates continuously increased and the mice successfully learned the task during three weeks training. We expect to find out neural mechanisms of sequential bimanual coordination using this rodent behavioral model with calcium imaging, single unit recording, and optogenetics.

Disclosures: M. Jeong: None. **Y. Kim:** None. **D. Kim:** None.

Poster

153. Posture and Gait: Higher-Order Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 153.01/KK4

Topic: E.06. Posture and Gait

Support: T32-HD007414-22

R37-NS090601

Title: Savings of motor and perceptual components of learning over multiple days of walking training

Authors: *K. A. LEECH[1], K. DAY[2], A. J. BASTIAN[3]
[1]Neurosci., [2]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [3]KKI & Johns Hopkins, Baltimore, MD

Abstract: Motor learning is not a single process—instead, several distinct mechanisms are thought to contribute to it. One such mechanism is error-driven ‘adaptation,’ in which a movement is partially corrected trial-by-trial until the desired pattern is produced. An interesting feature of adaptation is that it leads to a *sensorimotor* recalibration, so that individuals not only change a given movement, but also how they perceive that movement. For example, when a person adapts their walking pattern on a split-belt treadmill (where one belt moves faster than the other) they slowly correct their limping pattern step-by-step and also begin to perceive that their legs are moving at the same speed. Importantly, when the treadmill belts are returned to normal following adaptation, people walk with a limp (a motor aftereffect) and one belt now feels faster than the other, despite the fact that they are equal speeds (a perceptual aftereffect). Subjects must de-adapt in order to re-establish their normal motor and perceptual state.Another important feature of motor learning is that it can be built upon from one practice session to the next, a

phenomenon referred to as ‘savings’. Currently, there is no consensus about how different motor learning processes contribute to savings. We also do not understand savings of the perceptual component of adaptation, which is thought to be a marker of the error-driven mechanism.Here we studied if the motor and perceptual components of adaptation are saved across a 5-day split-belt walking paradigm. Each day, subjects performed a perceptual task to assess whether their leg speeds felt the same or different, adapted to the split-belt treadmill, and then performed the same perceptual task repeatedly as they de-adapted. Results showed that participants adapt and de-adapt their motor pattern faster from one day to the next, so that by day 5 they are able to switch back and forth rapidly between the split-belt and normal walking patterns. In other words, minimal motor adaptation or de-adaptation was required. The perceptual recalibration also changed over days: it was strongest on day 1, gradually decreased from days 1-3, but was never fully abolished by day 5. Thus, even though subjects could switch readily between motor patterns for split-belt and regular walking, they still showed a small perceptual aftereffect on day 5. These results suggest two alternatives. There may be a sensory-perceptual component of learning that has not been previously appreciated in this task. Or, error-driven sensorimotor adaptation is still working even when subjects appear to be able to “switch” motor patterns after 5 days of practice. T32-HD007414-22 to KAL and R37-NS090601 to AJB

Disclosures: **K.A. Leech:** None. **K. Day:** None. **A.J. Bastian:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

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Title: Modeling predictive and emergent processes in obstacle avoidance during locomotion

Authors: *A. DAREKAR[1,2], V. GOUSSEV[2], B. J. MCFADYEN[3], A. LAMONTAGNE[1,2], J. FUNG[1,2]
[1]Sch. of Physical and Occup. Therapy, McGill Univ., Montreal, QC, Canada; [2]Feil & Oberfeld CRIR Res. Centre, Jewish Rehabil. Hosp. (CISSS Laval), Laval (Greater Montreal), QC, Canada; [3]Dept. of Rehabil., Laval Univ., Quebec, QC, Canada

Abstract: We have developed a mathematical model comprising of predictive and emergent components to analyze locomotor circumvention behaviors in healthy and post-stroke individuals. The predictive component facilitates distance estimation from moving obstacles at future spatial positions, particularly in the obstacle's vicinity. The emergent component uses the differential games model to express the dynamic interaction with an intersecting obstacle thus shaping the avoidance strategy. The obstacle influence is modelled by a Gaussian 2D distribution with flexible elliptical cross sections that vary through the trial depending on the proximity to the obstacle. Assuming that the observed locomotor strategy is optimal, the inverse problem for the reconstruction of the obstacle's influence can be solved, providing the exact parameters of the shape of the obstacle influence. This study explored the association between outcomes of the model and observed experimental outcomes in order to understand the relative roles of the predictive and emergent processes in shaping circumvention behaviour. Five healthy and five post-stroke participants were assessed while walking towards a central target and avoiding a virtual obstacle that was either stationary or approaching randomly from either head-on, or diagonally 30° (left/right) or remained stationary. The association between the predicted distance from the obstacle at the point of passing (PDP) and the observed distance at passing (ODP) was investigated, using separate linear regression models for each obstacle approach. The association between maximum change in the elliptical obstacle influence (OI; ratio of the long and short axis length) and the observed dynamic clearance (DC; average weighted distance from the obstacle throughout the avoidance strategy centred at the minimum distance) were investigated. The PDP was directly associated with ODP and accounted for ≥95% variance in the ODP in both healthy and post-stroke individuals. The change in OI was associated with DC for moving obstacles only. Further, in the case of moving obstacles, DC was maintained above PDP (~ 1 m) in all obstacle conditions by both healthy and post-stroke participants. The mathematical model supported by experimental data suggests that when encountered with moving obstacles, predictive processes may regulate the safe margin from the obstacle in close proximity. At distances greater than the safe margin, circumvention behaviours may be guided by emergent processes that regulate dynamic interaction with obstacles. This indicates that both predictive and emergent processes may interact cooperatively to shape obstacle circumvention.

Disclosures: A. Darekar: None. **V. Goussev:** None. **B.J. McFadyen:** None. **A. Lamontagne:** None. **J. Fung:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Program#/Poster#: 153.03/KK6

Topic: E.06. Posture and Gait

Title: The effects of object location perturbations on a combined gait and prehension task

Authors: *G. C. BELLINGER[1], K. A. PICKETT[2], A. H. MASON[2]
[1]Interdepartmental Neurosci. (NUIN), Northwestern Univ., Chicago, IL; [2]Kinesiology, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Perturbations facilitate exploration of how humans adjust pre-planned motor patterns in response to unexpected changes in task requirements. In the current study target location was perturbed either closer to or further from participants as they walked toward the object to grasp it. *Methods:* Eighteen right-handed young adults (8 males, *M* = 23.38 years) participated in the study. Ten markers were placed on the chest and right arm. Three-dimensional motion capture data was collected at 120 Hz using a VisualEyez camera system and gait characteristics were collected using a GAITRite instrumented walkway. The target objects were three translucent dowels placed 20 cm apart on a support surface to the right of the mat. Target perturbation was achieved by shifting the LED illumination of the objects, which was triggered by the disruption of a light sensor placed two estimated step lengths before the central dowel. Participants stood 4.5 m from the center target and were instructed to walk towards the object, pick it up, and continue walking. The participants first completed 10 trials for each of the three object locations. This was followed by 60 trials during which the central dowel was always initially illuminated. In 10 of these trials the object was displaced toward the participant and in another 10 trials the object was displaced away from the participant. The markers on the nail beds of the index finger and thumb were used to calculate peak resultant aperture. The GAITRite system was used to quantify cadence, normalized velocity, normalized base of support, step-extremity ratio, and percentage of the gait cycle spent in double support in the two steps preceding object contact. A repeated-measures ANOVA with trial type as a within-subjects factor was performed for each variable. The three trial types of interest were guaranteed stationary center (GSC), perturbed towards (PT), and perturbed away (PA). *Results:* Post-hoc analyses with correction found that cadence in the PA condition (*M* = 111.97) was significantly less than cadence in both the PT (*M* = 113.18) (*p* = 0.002) and GSC (*M* = 113.77) (*p* = 0.01) conditions. Similarly, step-extremity ratio in the PA condition (*M* = 0.721) was significantly greater than step-extremity ratio in both the PT (*M* = 0.699) (*p* = 0.01) and GSC (*M* = 0.704) (*p* = 0.028) conditions. There was not a significant main effect of condition on normalized base of support, normalized velocity, percentage of the gait cycle spent in double support, or peak aperture, though double peaks were present in the aperture profiles of perturbation trials. The results suggest that only select movement characteristics of the combined task are influenced by object location perturbations.

Disclosures: G.C. Bellinger: None. **K.A. Pickett:** None. **A.H. Mason:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Program#/Poster#: 153.04/KK7

Topic: E.06. Posture and Gait

Support: R37 NS090610

T32 HD007414-22

Title: Accumulation of savings over multiple days of walking training

Authors: *K. DAY[1,2], K. A. LEECH[1,2], R. T. ROEMMICH[1,2], A. J. BASTIAN[1,2]
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Abstract: Acquiring new movements requires the capacity of the nervous system to remember previously experienced motor patterns from prior training. For example, when learning a golf swing, we can build on the training from a previous practice session rather than start from scratch every time we go to the driving range. This faster re-learning after initial learning is termed 'savings'. Here we studied how savings contributes to learning a novel walking pattern over several days of practice. Building on previous work, we used a split-belt treadmill to engage an adaptive learning mechanism and explore the multiday dynamics of savings.
We predicted that repeated training across a couple days might improve learning through a cumulative savings process that leads to faster error correction. After many days of practice, this might further evolve into the formation of a separate context specific calibration that can be retrieved interchangeably to meet the demands of the new environment.
Here we studied these processes in a series of experiments. First, we introduced the same split-belt treadmill adaptation paradigm for 30 minutes for 5 consecutive days. We observed savings within the first 3 days of the training, but by day 5 participants were able to produce near-perfect performance when switching between split and tied-belt environments. Our analysis showed that this was due to their ability to shift specific elements of their stepping pattern to account for the split treadmill speeds from one day to the next. We then investigated whether different perturbation schedules could speed this process, so that individuals would require fewer days of training. We studied people training only on day 1, with either one split-belt exposure, or adapting four times between split-belt and tied belt conditions to match the number of exposures in the first, multiday training group. Both of these single day training groups were tested again on day 5. Compared to one exposure, adapting four times within a day improved the performance on day 5. However, this group did not reach the level of performance as our multiday training group, because they could not perfectly switch between tied and split-belts.
In sum, it appears that people can transition from 'saving' a walking pattern to being able to rapidly switch between two walking patterns after 5 days of practice. Our initial attempt to speed this process over fewer days produced promising, though partial effects. Finally, a computational analysis of this process is underway to predict how to facilitate formation of a new walking pattern using repeated adaptive learning sessions.
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Disclosures: K. Day: None. **K.A. Leech:** None. **R.T. Roemmich:** None. **A.J. Bastian:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Program#/Poster#: 153.05/KK8

Topic: E.06. Posture and Gait

Support: Bevica Foundation

Title: Cognitive processing for step precision increases beta and gamma modulation during overground walking

Authors: *A. S.-C. OLIVEIRA, F. G. ARGUISSAIN, O. K. ANDERSEN
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Abstract: Safe overground walking requires constant evaluation of the environment and alternative strategies are needed to ambulate on uneven terrain, obstacles or wet floors. It is believed that overground displacement involves a combination of cognitive processing, sensorimotor integration and postural control. However, the influence of cognitive processing when defining the optimal overground walking trajectory is still unclear. In this study, we investigated whether human electrocortical activity changed during walking while following simple or complex movement pathways. We hypothesized that individuals walking through complex pathways would present slower walking speed and increased brain activity in cognitive and sensorimotor areas when compared to simple pathways. In this regard, ten healthy adults (21-36 years) were asked to walk overground (~120 gait cycles) in three different randomized conditions: 1) normal walking in a straight path (NW); 2) walking in a pre-defined pathway forcing variation in step width and length, in which each step was determined by a green mark (8×4 cm) on the floor (W1C), and 3) walking in the same pre-defined W1C pathway, however the place for each step would vary depending on the combination of three different colors (green, yellow and red) (W2C). In W2C, for each step the subject had to follow these rules: green+yellow = step on yellow, green+red = step on green and green+yellow+red = step on red, adding a cognitive decision process between each step. Walking speed and scalp electroencephalography (EEG) were recorded during the three conditions. Walking speed in W2C was significantly slower compared to W1C (~26%, $p<0.001$), suggesting that cognitive processing for evaluating the correct foot placement influenced walking pattern. Moreover, there was a significant effect of the condition on the absolute power for EEG channels FCz, C3, C4 and Cz ($p<0.05$). Power during W1C was ~60% and ~100% higher than NW for the beta and gamma band, respectively. Moreover, power during W2C was ~30% and ~70% higher than W1C for the beta and gamma band, respectively. These results suggest that complex environmental conditions demand higher brain activity in areas related to motor control. In addition, cognitive processing for defining body displacement directly interferes with the

walking modulation and cause reduction in the locomotor speed in W2C. This protocol can be relevant for underpinning changes in motor control and cognition related to aging and neurodegenerative diseases towards overcoming challenges faced in real-world scenarios.

Disclosures: A.S. Oliveira: None. **F.G. Arguissain:** None. **O.K. Andersen:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

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Title: Using a dual learning paradigm to simultaneously train multiple components of walking in people with stroke

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Abstract: Walking is a complex motor pattern consisting of multiple, distinct kinematic components. Abnormal gait can arise from dysfunction of one or several of these components simultaneously. After cerebral stroke, for instance, many patients experience a *step length asymmetry*, where one leg advances further than the other, as well as *stiff-knee gait*, where the paretic leg has insufficient knee flexion - resulting in a circumducted leg swing. These two components of gait dysfunction are distinct. Because of this, traditional rehabilitation practice focuses on one component at a time, leading to additional rehabilitation time to correct each component individually. Recent work from our lab, however, has demonstrated that neurologically-intact individuals can simultaneously adapt multiple components of the walking pattern, without interference. Here, we asked whether a similar dual-learning paradigm can be used to simultaneously train multiple, impaired components of walking in people after stroke. Individuals with chronic stroke completed a dual-learning task during which they simultaneously trained step length asymmetry and peak knee flexion components of walking. Step length asymmetry was trained using a split belt-treadmill where one leg moved twice as fast as the other. Knee flexion was trained via a joint angle learning task that provided biased visual feedback of sagittal knee flexion angles of the paretic leg during walking.
Preliminary results show that, like neurologically-intact adults, people with stroke can simultaneously adapt to a split-belt treadmill while performing a joint angle learning task to

increase paretic knee flexion. Specifically, all patients had motor aftereffects of more symmetrical step lengths when returning to tied-belt walking after a period of split-belt walking. We also found that some patients additionally retained the new knee flexion pattern that was achieved once the knee flexion visual feedback was removed. Thus, some patients can learn to correct two components of their faulty walking pattern simultaneously. This may suggest that in certain individuals after stroke, rehabilitation can be structured to alleviate multiple impairments in parallel via a dual adaptation learning paradigm - thus increasing rehabilitation efficiency.

Disclosures: K.M. Cherry-Allen: None. **M.A. Statton:** None. **P.A. Celnik:** None. **A.J. Bastian:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: This study was supported by CAMRI at Baylor College of Medicine grant to PJP

Title: Role of supplementary motor area in postural control

Authors: *R. GOEL[1], S. NAKAGOME[1], R. A. OZDEMIR[4], N. RAO[2], J. L. CONTRERAS-VIDAL, Ph.D.[3], P. J. PARIKH[1]
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Abstract: Postural control is one of the most fundamental motor tasks of human performance. Recently, the fronto-parietal regions have been found to be involved in postural control. The involvement of cortex has been primarily observed during maintenance of an upright stance following an unexpected movement of the support surface in able-bodied individuals. Specifically, the supplementary motor area (SMA); an area known to be involved with volitional action planning, is suggested to play a role in balance recovery. However, the functional role of SMA during postural responses remains to be known. In this study, we determined whether the integrity of SMA is important for postural responses to challenging sensory conditions in young able-bodied individuals. An MRI-guided continuous theta burst stimulation (cTBS) was used to transiently disrupt the SMA region. Ten young healthy subjects (6 males, 4 females) received the standard cTBS while additional ten young healthy subjects (6 males, 4 females) received placebo cTBS (sham). Following 40s of cTBS or sham-cTBS, subjects performed a continuous posture task with eyes-closed and with or without sway-referenced platform. The posture task consisted of three different levels of balance difficulties (low, medium, high). Further, to investigate the

electrophysiological changes following cTBS, we also assessed the cortical activity using electroencephalography (EEG) while subjects stood quietly (baseline; B) with eyes-closed before (B1), 10 min after (B2), and 30 min after (B3), cTBS. Following standard cTBS, the EEG spectral power in the fronto-central region increased significantly in delta, theta, alpha, beta, and gamma frequency bands at B2 with respect to B1, and returned to B1 level by B3 in all but beta and gamma bands. There was no difference in the spectral power during baseline EEG measurements in the sham group. As expected the postural performance worsened during the high-difficulty condition when compared with medium and low-difficulty conditions. Importantly, the impairment in the postural performance during the high-difficulty condition was significantly greater following standard cTBS than sham cTBS. We did not find a difference in postural performance between cTBS and sham cTBS groups for low- to medium-difficulty conditions. Our findings suggest that SMA, as evidenced by increased gamma power, is critical in the maintenance of an upright stance, albeit, during most challenging postural conditions. Moreover, SMA outflow to other cortical areas, including parietal cortex (see companion poster), may be sub-served by beta waves.

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Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: This study was supported by CAMRI at Baylor College of Medicine grant to PJP

Title: Modulation of fronto-parietal networks during adjustments to challenging postural conditions

Authors: *S. NAKAGOME[1,2], R. GOEL[1], P. J. PARIKH[1], J. L. CONTRERAS-VIDAL, Ph.D.[2]
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Abstract: Despite the importance of correcting posture to avoid falls when the balance is disturbed, there is still a debate about the underlying neural networks for postural control. In this study, we investigated the neural networks involved in postural adjustments during challenging postural conditions. Healthy subjects (experimental group n = 10; control group n = 10) were required to maintain balance continuously for 4 minutes while their brain activity was recorded using active electrode electroencephalography (EEG) after 40 seconds of continuous theta burst stimulation (cTBS) applied to the supplementary motor area (SMA), or sham cTBS. Electrode locations were digitized using a 3D tracking camera. Subjects were instructed to maintain

balance with their eyes closed while the support surface swayed in different proportions of body sway. The posture task consisted of nine conditions, each of which were 20 seconds long interspersed with rest periods of approximately 5-8 seconds. Dipole fitting method was used on independent components of EEG activity recorded during the posture task, and the dipoles were clustered using k-means algorithm (optimal k = 6) to identify brain sources during postural adjustments. Several brain regions were identified in both groups: cingulate gyrus (CG), anterior cingulate gyrus (ACG), medial frontal Gyrus (MFG), precuneus, cerebellum, lingual gyrus, parahippocampal gyrus and sub-gyral (SG). Event-related spectral perturbation (ERSP) analyses on each of the clusters showed ACG and MFG involvement as a significant increase (p-value threshold of 0.05) in power in delta-theta (1 – 7 Hz) and low gamma (30 – 50 Hz) bands. Precuneus showed a significant decrease in alpha (8 – 12 Hz) band in both groups and an increase in low gamma band only in the sham group. CG showed a significant decrease in alpha-beta (8 – 30Hz) and an increase in delta and low gamma in both groups. SG showed a decrease in alpha in both groups, but an increase in low gamma in the sham group only. Overall, the cTBS group showed a significant increase in delta-theta in prefrontal cortex suggesting greater attentional and error correction resources to overcome cortical suppression due to cTBS, while the sham group had an increase in low gamma in precuneus and SG indicating a critical role for these structures during postural adjustments. Refer to a companion poster that discusses the effects of cTBS over SMA on postural performance.

Disclosures: S. Nakagome: None. **R. Goel:** None. **P.J. Parikh:** None. **J.L. Contreras-Vidal:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: NSF #1264752

UMass Faculty Research Grant

UMass IMSD

Title: Generalization of split-belt treadmill adaptation: Motorized treadmill after-effects are preserved after washout on a non-motorized treadmill

Authors: D. L. GREGORY, F. C. SUP, *J. T. CHOI
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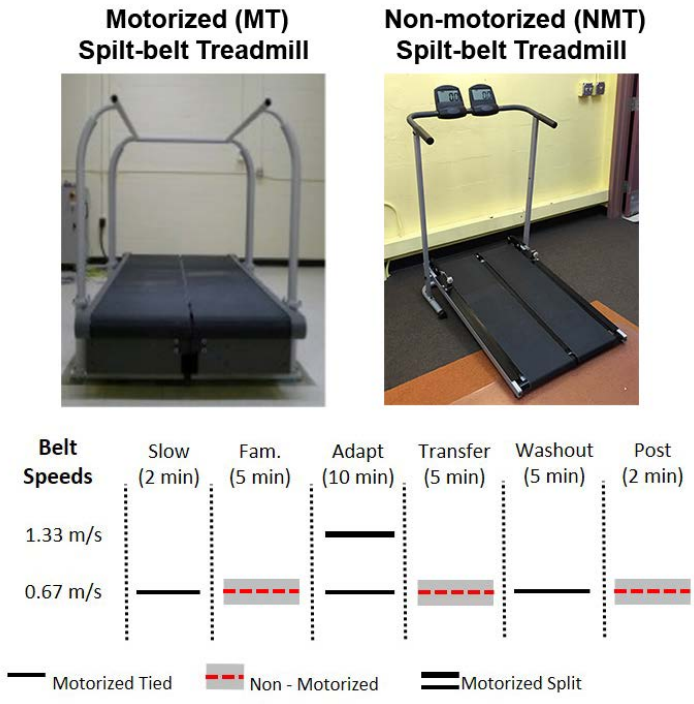
Abstract: Introduction: Split-belt treadmills can be used to induce locomotor adaptation, a form of sensorimotor learning that has become an important concept in gait rehabilitation. The objective of this study is to determine whether adaptation on a motorized split-belt treadmill (MT) transfers to walking on a non-motorized split-belt treadmill (NMT). If so, it may be possible to utilize a low-cost NMT for long-term training in a home-based setting to enhance training effects. **Methods:** We designed and built a self-regulated non-motorized split-belt treadmill with symmetrically resisted but independently controlled belts (Fig. 1). During Adaptation, subjects walked at a 2:1 speed perturbation (0.67 m/s; 1.33 m/s) on the MT. To assess after-effects, subjects walked at preferred speed on the NMT during Transfer, and at the slow speed (0.67 m/s) on the MT during Washout. Kinematics was calculated from the position of reflective markers placed on the ankle (lateral malleolus) bilaterally. Electromyography (EMG) was collected from the medial gastrocnemius (MG) muscles. Step-length and double support symmetry were calculated for each stride. Transfer and washout indexes were calculated as the ratio of the magnitude of after-effects relative to the magnitude of split-belt learning. **Results:** During Transfer, subjects showed pronounced after-effects on the NMT (transfer index: double support = 0.87±0.65, step-length = 0.9±0.7) that gradually faded. Upon returning to the MT during Washout, after-effects persisted (washout index: double support = 1.32±0.68, step length = 1.38±0.93) and gradually washed out. There were no after-effects on the return to the NMT. During Transfer, the slow MG activity increased while the fast MG activity decreased around mid-stance (20% - 40% stride cycle). During Washout, after-effects in the MG were expressed as initial bursts in the first 20% of the stride cycle. **Conclusions**: Robust kinematics and EMG after-effects during NMT walking demonstrates that a low-cost split-belt NMT may be useful as part of a gait re-training protocol.



Disclosures: D.L. Gregory: None. **F.C. Sup:** None. **J.T. Choi:** None.

Poster

153. Posture and Gait: Higher-Order Control

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 153.10/KK13

Topic: E.06. Posture and Gait

Title: Corticospinal drive to tibialis anterior muscle during split-belt treadmill walking

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Abstract: Introduction: In healthy subjects, motor units from the tibialis anterior (TA) muscle receive a common synaptic drive that is modulated during the walking cycle. Coupling of motor unit activities, characterized by coherence peaks between 15-30 Hz, is related to the functional contribution of the corticospinal tract to the control of gait. Interestingly, changes in the strength of coherence with gait training has been linked to improvements in gait function. Here we investigated whether walking on a split-belt treadmill induces changes in corticospinal drive to ankle muscles on both legs. **Methods**: Healthy young adults walked on a split-belt treadmill. We recorded kinematics using reflective markers placed on the lower limbs, and electromyography (EMG) using two pairs of surface electrodes placed at the most proximal and distal ends of the TA muscle. Each session consisted of a pre-adaptation period, adaptation period, and post-adaptation period. During the pre-adaptation period, subjects walked symmetrically at a slow (0.5 m/s) and a fast (1.0 m/s) speed for 3 minutes each. During the adaptation period, walking was challenged by altering the speed of each leg at a 1:2 speed ratio (0.5 m/s for the slow belt, 1.0 m/s for the fast belt) for 15 minutes. During the post-adaptation period, subjects walked with both legs at 0.5 m/s for 10 minutes. **Results**: Coherence in the 15-30 Hz (beta) and 30-50 Hz (gamma) frequency band was observed between the EMGs recorded from the proximal and distal TA during early swing phase (around 400 ms before heel strike). In the beta frequency band, coherence was increased during split-belt walking compared to tied-belt conditions. In the gamma band, coherence was greater during early adaptation compared to late adaptation and was greater in the early post-adaptation compared to late post-adaptation. **Conclusions**: Corticospinal drive to ankle muscles is altered during split-belt walking. Data suggests that the coherence in the gamma frequency band may reflect adjustments needed in changing environments. The increase in beta band frequency during adaptation period suggests that there is an increased involvement of the corticospinal tract during split-belt treadmill walking.

Disclosures: S. Sato: None. **J.T. Choi:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: LASPAU/CAPES BEX 13722-13-1

Title: Perceptual and motor learning of locomotor skills

Authors: *G. BORIN, J. T. CHOI
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Abstract: Introduction: Perception and locomotor pattern generation must be properly integrated for successful navigation. Practicing complex locomotor skills, such as those involving sequencing, may engage distinct mechanisms that support perceptual and motor learning. We have recently shown that healthy participants can learn a specific sequence of step length during visually guided walking. Performance improved more with a repeating sequence compared to a random sequence, suggesting that subjects either learned the sequence of visual stimuli (perceptual learning), or the sequence of motor responses (motor learning), or both to plan and control precise foot placement. The objective of this study is to develop and use a new paradigm to dissociate perceptual vs. motor learning of locomotor skills. **Methods**: Ten healthy young subjects performed a visuomotor task during treadmill walking. Visual targets were displayed on a screen in front of the treadmill. The targets instructed subjects how to change step length (e.g., short, medium, long) from one stride to the next. The Training involved practicing a non-repeating series as well as a repeating series of step length adjustments (i.e., short-long-normal-long-short-normal) over (R)andom and (S)equence blocks, respectively. To measure perceptual learning, subjects were re-tested with the same non-repeating and repeating sequences during backward walking (i.e., the visual stimulus was the same, but the movement response was different). To measure motor learning, subjects were re-tested with the visual display inverted during forward walking (i.e, the visual stimulus was different but the leg movement was the same). **Results**: During Training, subjects performed better on Sequence compared to Random blocks (sequence-specific learning: S - R = 11 ± 2.2 points). If sequence-specific learning is purely based on memory of the sequence of visual targets (perceptual learning), then using a different walking pattern to perform the task should not affect performance. We found that during Perceptual testing, 6/10 subjects performed better on Sequence compared to Random blocks (S - R = 4 ± 3.4 points). If the sequence-specific learning is purely based on memory of the sequence of movement responses (motor learning), then performance should remain the same when the visual sequence is flipped but the movement pattern is unaltered. We found that during Motor testing, 8/10 subjects performed better on Sequence compared to Random blocks (S - R =

10 ± 3.9 points). **Conclusions**: There are parallel but independent processes that contribute to the perceptual and motor learning of locomotor sequences.

Disclosures: G. Borin: None. **J.T. Choi:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: AHA Grant

Title: "Look out!": Using environmental cues to retrieve appropriate gait patterns

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Abstract: Over our lifetimes, we learn and store many variations of simple walking patterns. We may have different patterns for walking on sand or ice; with experience, we can learn to switch between these patterns when needed. With aging, the ability to switch between different locomotor patterns is compromised, which may contribute to increased risk of falling when the environment changes. Our objective was to determine whether a verbal warning can help people retrieve an appropriate gait pattern for a particular walking condition. We hypothesized that verbal cues would help individuals adapt faster to a change in walking environment. To introduce a new walking condition in a controlled setting, we used a split-belt treadmill, which has two belts that can drive each leg at different speeds. On Day 1 of the experiment, young adult participants walked on the treadmill, alternating between tied-belt (belts running the same speed; i.e., "normal" walking) and split-belt (belts running at different speeds) conditions. During this time, participants learned different gait patterns for tied- and split-belt walking. On Day 2, participants were re-exposed to tied-belts and split-belts to determine how well they retrieved the walking patterns they learned on Day 1. Half of the participants were told whether the belts would be tied or split immediately preceding each trial; the other half was given no information. Using a Vicon motion analysis system to capture and quantify walking kinematics, we determined that advance warning had no effect on how well people walked on tied- or split-belts on Day 2. Such results suggest that young adults retrieve gait patterns primarily based on sensory feedback (e.g. feeling how the belts are moving the legs) rather than explicit information about the walking environment. Future work will examine how older adults use explicit information to adjust walking coordination.

Disclosures: E.V. Pullen: None. **E.V. Vasudevan:** None.

Poster

153. Posture and Gait: Higher-Order Control

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NIH Grant R01- AG049735

Title: Multi-objective control of lateral foot placement while walking

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Abstract: Falls are common and perilous events for the elderly. When they walk, humans are inherently more unstable side-to-side (laterally). Additionally, humans most often walk on paths (sidewalks, store aisles, etc.) with finite width. It is unclear how people regulate lateral stepping movements in such contexts. Here, we extend a computational framework (Dingwell et al., PLoS Comput. Biol., 2010; John et al., PLoS Comput. Biol., 2016) to determine how humans exploit available redundancies to achieve these tasks. Due to biomechanical redundancy, there are infinite choices for where to place each foot at each step. We presume the left and right feet act as end-effectors that enact control. We show that all strategies to control lateral stepping on any defined path can be constructed from some combination of position (P), heading (H), and/or step width (W) control. Models that control only a single variable (P, H, or W) do *not* replicate what humans do. Likewise, one cannot optimally control any 2 of these variables simultaneously because each control policy predicts a different foot placement and you cannot put your foot in 2 places at the same time. Here, we derived *multi*-objective control models of lateral stepping that trade-off control of any 2 of these 3 candidate control variables. Stochastic control computational models were developed from pre-defined goal functions (Cusumano & Dingwell, Hum. Mov. Sci., 2013) that tried to simultaneously minimize errors with respect to any 2 of the 3 candidate control variables. Control inputs for each candidate stepping model were derived analytically. The resulting controllers then enacted each new step as a weighted average of the 2 foot placements predicted by each individual controller. For each possible pair of 2 candidate control variables (P, H, & W), we varied the relative weighting (from 0% to 100%) of which was controlled more and simulated walking for twenty trials of 1000 steps each. In parallel experiments, humans exhibited variability in all stepping variables. Control models that tried to control either (H & P) or (H & W) failed to replicate experimental findings, regardless of the

relative proportion of control. However, the model that traded-off control of (P & W) replicated all relevant experimental stepping dynamics when the proportion of control was weighted ~85%-95% towards W-control. This approach yielded directly testable predictions that demonstrate humans adopt multi-objective lateral stepping control that prioritizes W, while trading-off some W-control to maintain lateral P-control. Prioritizing step width helps maintain lateral balance, which is highly relevant for those prone to falling.

Disclosures: **J.B. Dingwell:** None. **J.P. Cusumano:** None.

Poster

153. Posture and Gait: Higher-Order Control

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Topic: E.06. Posture and Gait

Support: NIH Grant RO1HD078330

Foundation of Physical Therapy, Florence P. Kendall Scholarship

Title: Impact of cognitive information of transfer of locomotor learning

Authors: ***M. FRENCH**[1], D. S. REISMAN[2]
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Abstract: Background: The theory of credit assignment suggests that if an individual assigns an error to the environment, the learned response to this error will not transfer to a new environment, while if the error is assigned to themselves, individuals will transfer the learned response. Previous work has found that many factors influence error assignment during reaching and lifting; however, this has not been investigated in the complex, whole-body task of walking. Thus, this study aims to evaluate the impact of cognitive information on the transfer of a new locomotor skill from the treadmill to over ground walking. Methods: Healthy adults (21-40 years) performed the following walking activities: 1) over ground baseline (OG_{base}) 2) treadmill baseline (TM_{base}) 3) 10 minutes treadmill with distorted visual feedback about step length (SL, DVF_{pre}) 4) 30 seconds treadmill with no feedback (Catch) 5) 5 minutes treadmill with distorted feedback (DVF_{post}) 6) over ground (OG_{post}). During DVF_{pre} and DVF_{post}, feedback of each leg's SL was gradually distorted by 9%; the displayed SL of the right leg was longer than actual SL and the displayed SL of the left leg was shorter. Subjects were randomized into 2 groups. The explicit group (EXP) was told that the feedback was distorted and instructed to keep the bars symmetric. The implicit group (IMP) was only told that the bars represented SL. Step symmetry [SS, $(SL_{Left}-SL_{Right})/(SL_{Left}+SL_{Right})$] was quantified during all phases, with 0 representing symmetry. Percent adaptation [$(SS_{DVFpost}-SS_{TMbase})*100$] was used to determine the extent of

adaptation. After-effects (SS_{DVFpre}-SS_{catch}) and transfer index [(SS_{OGpre}-SS_{OGpost})/(SS_{DVFpre}-SS_{catch})] were calculated to determine how much of the new pattern was retained and transferred respectively. Results: Based on preliminary data (n=6, 24.8 ± 5.9 years), both groups adapted their SL to the distorted feedback, resulting in an asymmetric walking pattern; however, EXP (n=3) adapted more than IMP (n=3) (8.25 ± 1.21% and 5.34 ± 1.81%, respectively). There does not appear to be a difference between groups in retention (0.06±0.02 and 0.04±0.01, respectively). EXP transferred less of the newly learned pattern to over ground than IMP (0.02±0.27 and 0.25±0.06, respectively, where a smaller value represents less transfer during OG_{post}). Discussion: While results are preliminary, it appears that the cognitive information provided prior to a locomotor learning task can impact the extent of adaptation and the amount transferred. It appears that knowing that an error is caused by the environment leads individuals to adapt more fully to the new pattern; however, limits transfer as hypothesized.

Disclosures: M. French: None. **D.S. Reisman:** None.

Poster

154. Reflexes and Reflex Modulation

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Topic: E.06. Posture and Gait

Support: NIH grant K12HD055931

NIH grant K01 HD079584

Title: Characterizing short and long latency TMS-conditioning of H-reflexes

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[1]Physical Therapy, 1441 Clifton Rd NE, Room 205, Atlanta, GA; [2]Rehabil. Med., [3]Emory Univ., Atlanta, GA

Abstract: Introduction: Combining peripheral electrical stimulation of the soleus with transcranial magnetic stimulation (TMS) at varying latencies can be used to evaluate descending corticospinal influences on spinal reflex excitability. Short-latency facilitation (SLF) probes the excitability of direct descending projections, while long-latency facilitation (LLF) evaluates indirect, polysynaptic descending projections. Previous studies have determined SLF and LLF at a single, presumably optimal stimulation intensity (H-reflex amplitude of 20% of Mmax) (Gray, et al, 2017). However, whether SLF and LLF occur at other points on the H-reflex recruitment curve is unknown. The purpose of this study was to evaluate SLF and LLF at a range of stimulation intensities along the H-reflex recruitment curve. Methods: Ten young, neurologically intact, adult participants participated in a single experimental session. Unconditioned H-reflex

recruitment curves were obtained by delivering peripheral nerve stimulation to the posterior tibial nerve at 30 different stimulation intensities ranging from 40% below H-reflex threshold to 20% above Mmax. We evaluated whether or not the H-reflex recruitment curve was modulated at varying points across the curve (H reflex amplitude at 20% of Mmax, Hmax, sub-Hmax, and supra-Hmax) for the TMS-conditioned H-reflexes (SLF and LLF). For SLF, TMS was delivered over the soleus motor cortex hotspot 1.5ms following peripheral nerve stimulation. For LLF, TMS was delivered 10-ms before peripheral stimulation. Subthreshold TMS (90% of resting motor threshold) was delivered for both intensities. A 2-way ANOVA with post-hoc tests was performed to evaluate the effect of conditioning type and stimulation intensity. Results: Our results showed that compared to unconditioned H-reflex amplitudes (0.42±0.21 %Mmax), significantly larger H-reflexes were obtained during the SLF (0.50±0.20 %Mmax; p=0.07) and LLF protocols (0.63±0.21 %Mmax; p=0.001). Additionally, SLF and LLF H-reflex curves demonstrated a leftward shift compared to the unconditioned curve. Discussion: Our findings demonstrate that evaluating SLF and LLF over a range of stimulation intensities (i.e. ascending limb and peak of the H-reflex recruitment curve) may provide a more comprehensive measure of SLF and LLF compared to assessment at a single intensity. In conjunction with common measures of cortical and spinal excitability, SLF and LLF offer additional insights into mechanisms underlying neurologic injuries such as multiple sclerosis or stroke.

Disclosures: T.M. Kesar: None. **M. Hoque:** None. **C. McMullen:** None. **M.R. Borich:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.02/KK19

Topic: E.06. Posture and Gait

Title: H-reflex modulation as a function of sloped support surfaces

Authors: *R. L. SEGAL[1], A. DUTT-MAZUMDER[2], A. THOMPSON[3]
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Abstract: The soleus H-reflex is task- and posture-dependently modulated (Pinniger et al., 2001). Further, passively imposed changed ankle angles affect the H-reflex and M-wave recruitment in sitting subjects (Frigon et al., 2007). However, to date, the interaction of active motor task and additional joint factors on the reflex behaviours is not understood. Thus, in this study, we investigated the effects of different surface slopes, which naturally imposed certain joint angles at the ankle, on the soleus H-reflex during standing.
In twelve neurologically normal subjects, the *soleus* H-reflex and M-wave recruitment curves were measured while subjects maintained upright standing posture on 3 different angles of

slopes: -15° down (ankle plantarflexion), +15° up (ankle dorsiflexion), and 0° (neutral). In the first experiment, the subject stood with both the studied leg and contralateral leg loaded (i.e., weight bearing with both legs). In the second experiment, the subject stood with the studied leg unloaded (i.e., the whole weight was on the contralateral leg). The *soleus* and its antagonist tibialis anterior background EMG activity was maintained across all 3 support surface conditions in each experiment. We quantified how the different slope angles that imposed specific joint angles at the ankle influenced the H-reflex excitability and the M-wave measurement.
In both experiments (i.e., the test leg loaded and unloaded), three slope conditions produced three distinctive ankle joint angles in standing subjects; 15±1° plantarflexion for the -15° down condition, 15±1° dorsiflexion for the +15° up condition, and 0° for the neutral condition. The slope conditions significantly influenced the M_{max} (mV), H_{max} (mV), and H_{max}/M_{max} ratio; all three measures were significantly larger in the -15°down condition (p <0.05) than with 0° flat or +15° up conditions (H_{max}/M_{max} ratio: 0.5, 0.4, and 0.4 for -15°down, 0° flat, and +15° up, respectively). Larger differences across the slope conditions were found in the second experiment (i.e., leg unloaded); H_{max}/M_{max} ratio: 0.4, 0.3, and 0.2 for -15°down, 0° flat, and +15° up, respectively.
The study results indicate significant interactions of imposed ankle joint angles and weight-bearing conditions during standing. The limited extent of joint angle influence on the H-reflex compared to the previous study in sitting subjects may imply the presence of strong task-dependent effects during standing in determining the H-reflex excitability.

Disclosures: R.L. Segal: None. **A. Dutt-Mazumder:** None. **A. Thompson:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.03/KK20

Topic: E.06. Posture and Gait

Title: Morphological and reflex properties of soleus during ankle flexion

Authors: *A. DUTT-MAZUMDER[1], R. L. SEGAL[1], L. DAVIS[2], A. K. THOMPSON[3], J. DEAN[1]
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Abstract: Length-tension relationship of the muscle is well known. However, to date, the relationships among the muscle length, reflex amplitude, and reflex-generated torque have not been investigated. In this study, we aimed to examine the relationships between the H-reflex, reflex-generated ankle torque, and fascicle length in the soleus muscle across different ankle joint angles. We hypothesized that normalized H-reflex size would be inversely related to ankle

torque and fascicle length. Experiments were performed in eleven neurologically healthy subjects while seated comfortably on a dynamometer (Biodex®). The soleus fascicle length, H-reflex and M-wave recruitment curve, and ankle joint torque were measured with the hip and knee joint angles fixed at 120° while the ankle joint angles ranged from +15°(ankle dorsiflexion), to -30°(ankle plantarflexion), in increments of 15°. Across all ankle angle conditions, background EMG were maintained stable at resting level for soleus, tibialis anterior, lateral and medial gastrocnemius. H-reflex and M-wave recruitment curves were assessed in the soleus, where percutaneous stimulation elicited H_{max} was normalized to the M_{max} for a given ankle angle. The ankle torque measures were obtained from the dynamometer. Static long axis grayscale sonographic images of the soleus fascicle length and pennation angle were obtained with a 12 MHz linear array transducer (Logiq I, GE® Healthcare) positioned along the lateral aspect of the distal lower leg, posterior to the fibula. Superficial and deep fascial margins of the soleus as well as the distal myotendinous junction of the lateral gastrocnemius were used as frame of reference. When the ankle joint angle changed from a dorsiflexed position to a plantarflexed position, the M_{max} (mV), H_{max} (mV), and the H_{max}/M_{max} ratio significantly increased, while ankle torque and fascicle length significantly decreased ($p < 0.01$). **In other words, Hmax/Mmax was inversely related to soleus fascicle length and ankle torque**. For the first time, the study showed how muscle fascicle mechanics relate to the H-reflex and M-wave measurements as a function of ankle joint angles.

Disclosures: A. Dutt-Mazumder: None. **R.L. Segal:** None. **L. Davis:** None. **A.K. Thompson:** None. **J. Dean:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.04/KK21

Topic: E.06. Posture and Gait

Support: The Sasakawa Scientific Research Grant

Title: Prediction of postural perturbation modulates the corticospinal excitabilities in the ankle muscles

Authors: *K. FUJIO[1], H. OBATA[2], N. KAWASHIMA[3], K. NAKAZAWA[4]
[1]Chiba Prefectural Univ. of Hlth. Sci., Chiba-city/Chiba, Japan; [2]Kyushu Inst. of Technol., Kitakyushu-Shi, Japan; [3]Nat'l Rehab Ctr. Japan, Tokorozawa, Japan; [4]The Univ. of Tokyo, Tokyo, Japan

Abstract: Corticospinal pathways of the ankle dorsi- and plantar-flexion muscles are thought to be one of the key nodes for postural control. Previous researches suggest that the corticospinal

excitability is modulated depending on postural demands for ongoing balance control. However, it is still unclear whether those excitabilities would be modulated with prediction of postural deflection. The aim of this study was to clarify how the corticospinal excitabilities in the ankle muscles were modulated when subjects could predict upcoming perturbations. Twelve participants stood on the movable platform which translated anteriorly or posteriorly in horizontal plane. The electromyographic activities were recorded from the right tibialis anterior (TA) and the soleus (SOL) muscles. Motor-evoked potentials (MEPs) elicited by single-pulse transcranial magnetic stimulation were measured during standing. Three types of surface-translations, Low (3.5 cm, 10.0 cm/s, anteriorly), High (7.0 cm, 25.0cm/s, anteriorly), Posterior (7.0 cm, 25.0cm/s, posteriorly), were applied in separated blocks. The MEPs were obtained 50ms before the onset of perturbations during 5 conditions: No perturbation, Low, High, Posterior and Random conditions. In Random condition, the 3 perturbations were applied in random order. A one-way repeated measure ANOVA for perturbation types showed the main effect in the TA-MEP amplitude ($p<0.001$). Post hoc comparison revealed that the TA-MEPs in Low, High and Random conditions were significantly larger than in No perturbation condition (No perturbation vs Low, $p=0.013$; No perturbation vs High, $p=0.003$; No perturbation vs Random, $p=0.016$). Furthermore, the TA-MEP in High condition was significantly larger than in Low and Posterior conditions (High vs Low, $p=0.013$; High vs Posterior, $p=0.013$), suggesting that magnitude and direction of platform translation affect the corticospinal excitability of the TA just before perturbation. In the SOL, the significant main effect can be also appeared ($p = 0.03$). Our results showed that the corticospinal excitabilities in the ankle muscles are modulated beforehand based on the information about direction and magnitude of perturbation. It suggests that the central nervous system for postural control takes advantage of a future state of standing balance.

Disclosures: **K. Fujio:** None. **H. Obata:** None. **N. Kawashima:** None. **K. Nakazawa:** None.

Poster

154. Reflexes and Reflex Modulation

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.05/KK22

Topic: E.06. Posture and Gait

Support: EMBO ALTF 13-2015

NS080586

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P01 NS072031

Title: Dissecting the diversity of spinal circuits for distinct sensorimotor aversive behaviors

Authors: *G. GATTO, S. BOURANE, A. DALET, M. GOULDING
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Abstract: The broad repertoire of body movements that animals display is generated by the interplay of supraspinal motor control pathways and sensorimotor circuits in the spinal cord. Growing evidence supports a prominent role of dorsal spinal cord interneurons (dINs) in processing cutaneous and descending inputs. What is not known is how this information is integrated and conveyed to other elements of the motor system to shape the stereotyped movements animals generate in response to aversive stimuli. We are teasing out the neural circuits that underlie two distinct sensorimotor behaviors: the withdrawal reflex (induced either by noxious or mechanical stimuli) and the scratch reflex. By using the combinatorial application of optogenetic, pharmacological and intersectional genetics, we have identified selected populations of neurons that are specific to certain aversive responses. While dINs (i.e. CCK-expressing) are sufficient to trigger a noxious-induced withdrawal reflex by directly synapsing onto motor neurons, neurons that belong to the locomotor central pattern generator (i.e. Engrailed-expressing V1 INs) are necessary for the smooth performance of the cutaneous-induced withdrawal reflex and for scratching behavior. Spinal ablation or silencing of the V1 interneurons causes a strong reduction in the speed of scratching, and in the number of scratch bouts, as well as a reduced sensitivity to static and dynamic touch. The further characterization of the connectivity and functioning of these and other identified classes of INs will shed light on the logic underlying the withdrawal and pruritogenic reflex circuitry, and its convergence to, and divergence from the locomotor neural network. The further subdivision of these large IN populations into coherent smaller subgroups of neurons will allow us to determine the contribution genetically-defined interneuron cells types make to sensorimotor transformation in the spinal cord.

Disclosures: G. Gatto: None. **S. Bourane:** None. **A. Dalet:** None. **M. Goulding:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.06/KK23

Topic: E.06. Posture and Gait

Support: Jeffress Foundation

Title: The spinal nociceptive withdrawal response of the hind limb in the rat exhibits limited dependence on stimulus location

Authors: *C. L. CLELAND, C. E. ESQUIVEL, H. T. DAVIS
Biol., James Madison Univ., Harrisonburg, VA

Abstract: The nociceptive withdrawal response (NWR) of the limb is a protective, multi-joint movement in response to noxious stimulation of the limb. Previous studies in animal models, often based on EMGs, differed as to the dependence of the response direction and magnitude on stimulus location. The specific aim of our research was to use three-dimensional high-speed video to determine whether *movement* of the foot in response to heat stimuli delivered to the foot and lower leg depended on the location of the stimulus. In particular, we sought to determine whether the movement strategy was categorical (limited number of directions of movement) or continuous (direction of movement directly away from stimulus location, resulting in a large number of possible directions of movement). In spinalized male Sprague-Dawley rats, localized, nociceptive heat stimuli (980nm laser diode) were delivered along three dimensions—circumferentially around the lower leg, circumferentially around the foot and along the plantar surface of the foot. The response was quantified with two high-speed cameras which yielded three-dimensional movement trajectories. Our results demonstrate that in spite of a wide range of stimulus locations over the hind foot and leg, response directions were restricted to two—rostral/medial/dorsal and caudal/medial/dorsal—directions, consistent with a categorical strategy. Further, the preference for these two directions was also reflected in the distance of the movement, which was greatest for stimuli directly opposite the preferred response directions. However, significant but weak dependencies of response direction and distance on stimulus location were found for all three dimensions of stimulus application, supporting a continuous strategy. Together, our results demonstrate, based on movement analysis, that the NWR employs a hybrid categorical-continuous strategy that may minimize the harmful consequences of noxious stimuli.

Disclosures: C.L. Cleland: None. **C.E. Esquivel:** None. **H.T. Davis:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.07/KK24

Topic: E.06. Posture and Gait

Title: Decomposition of the tail nociceptive withdrawal response into combinations of movement primitives associated with individual muscles in the rat

Authors: *J. NGUYEN, C. L. CLELAND
Biol., James Madison Univ., Harrisonburg, VA

Abstract: In response to noxious stimuli, animals withdraw the affected body part using the nociceptive withdrawal response (NWR). The CNS may simplify control by reducing the number of muscular degrees of freedom through the use of muscle synergies. The rat tail, which contains a large number of hyper-redundant degrees of muscular freedom, presents a substantial computational challenge. The specific aim of our study is to identify possible muscle synergies in the distal portion of the tail that reduce the number of degrees of freedom by decomposing the behavioral NWR into combinations of movement primitives arising from contraction of individual muscles. Adult Sprague-Dawley male rats were loosely restrained in an acrylic tube and 14 evenly spaced black marks were placed on the dorsal surface of the distal half of the tail. Heat stimuli were delivered in random order to the lateral surface of the tail adjacent to each of the fourteen black marks with a laser diode (980nm) and the NWR was recorded using high-speed video (650 fps). Subsequently, the same rat was anaesthetized with pentobarbital (60 mg/kg i.p) and a 2 cm incision was made on the dorsal-lateral surface of the proximal tail. Individual long tendons arising from pelvic muscles (n=20-30) were identified and pulled rostrally to create tail movements, or "movement primitives", that were recorded by video. Computationally, the behavioral movements were decomposed into combinations of movement primitives to identify the mostly likely of patterns of muscle activity that could have given rise to the behaviorally recorded movement. Motor primitives were diverse, creating movements that resulted in focused tail bends distributed over the entire length of the distal tail. In contrast, behavioral responses to heat stimuli resulted in more complex movements of the tail, suggesting that multiple muscles in the pelvis contribute to the NWR of the tail. Ongoing studies should distinguish between alternate muscle strategies underlying the tail NWR.

Disclosures: J. Nguyen: None. **C.L. Cleland:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.08/KK25

Topic: E.06. Posture and Gait

Title: Contributions of A-delta nociceptors to the direction of the nociceptive withdrawal response in intact, unanesthetized rats

Authors: *K. M. SAMMONS, L. C. DEAK, Z. C. OKAFOR, C. L. CLELAND
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Rats rapidly withdraw their hind limb in response to heat or other noxious stimulation, which is known as the nociceptive withdrawal response (NWR). Two types of nociceptors may mediate the NWR, C-fibers and Aδ nociceptors. Among the differences between these two types of nociceptors, C-fibers have larger receptive fields than Aδ nociceptors. Previous studies from

our laboratory have shown that the direction of the NWR does not depend on stimulus location. However, in some experiments low rates of heating resulting in longer latencies may have predominantly stimulated C-fibers. If C-fibers were stimulated, we might expect limited dependence on stimulus location due to the larger receptive field of C-fibers. Therefore, it remains possible that Aδ nociceptors could mediate a response that is dependent upon stimulus location. The specific aim of our experiments was to determine if the direction of the NWR depends on stimulus location using high intensity, short duration (100ms) pulses of heat that have been shown to preferentially stimulate Aδ nociceptors. Five small (1 mm) spots (three aligned rostral-caudal, three aligned lateral-medial) were blackened on the plantar surface of the left hind paw of adult, male, intact and unanesthetized Sprague-Dawley rats. Rats were placed on a glass plate and loosely constrained in a fenestrated acrylic box. The blackened spots were stimulated with a focused 980nm laser diode in random order to evoke a NWR, in which the rat rapidly withdrew and then replaced its foot on the glass plate. The initial and final positions of the paw were recorded with a conventional camcorder (60 fps @ 1080p) placed underneath the rat. The difference between the initial and final positions represented the NWR movement response vector. Stimulus location still did not have an effect on the direction of the NWR in the rostral-caudal and lateral medial axes (n=6 rats, $p = 0.3, 0.5$ ANOVA), even after correcting for the effects of initial position of the foot ($p = 0.5, 0.5$, multiple linear regression). Rather, our results showed that the direction and magnitude of the response is determined only by the initial position of the paw (rostral-caudal $p < 0.00001$, lateral-medial 0.00001, Pearson correlation), as observed in our previous experiments using diverse rates of heating. Our findings reinforce the view that the direction of the NWR depends primarily on initial posture rather than stimulus location.

Disclosures: K.M. Sammons: None. **L.C. Deak:** None. **Z.C. Okafor:** None. **C.L. Cleland:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.09/KK26

Topic: E.06. Posture and Gait

Title: Postural movements accompany the heat evoked nociceptive withdrawal response in unrestrained rats

Authors: *S. MAVI, M. E. PEGELOW, D. A. GRIGORYAN, C. L. CLELAND
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Noxious stimulation evokes the nociceptive withdrawal response, in which the part of the body stimulated is moved away from the stimulus. Typically, rats are loosely restrained in a

boxes or tubes. However, there is limited research that evaluates the NWR of rats that are unrestrained. The impact of restraint is underscored by our earlier studies in lizards, which showed that as the heat stimulus location moves proximally closer to the base of the tail, the animal tends to walk forward instead of moving its tail. The specific aim of this study was identify and characterize postural changes that may accompany the NWR of the foot or tail in unrestrained rats. Male Sprague-Dawley rats (n=8) were briefly anesthetized (isoflurane) to mark their tail (five points distributed evenly along the length of the tail), feet (1-3 points on each of four feet), and body (rostral, caudal) for tracking and stimulation. Upon recovery from anesthesia, animals were centered on a 3'x3' glass table and heat stimuli were delivered in random order to one of the five stimulus locations on the tail or at a central point on one of the four paws. Movement was recorded through a conventional video camera placed below the glass table and subsequently tracked in software (Proanalyst). In addition to the expected tail or foot withdrawal, we observed concomitant body movement in 100% of trials. The direction of body movement consisted of both forward translation and rotation away from the stimulus, though neither timing ($p=0.37$, Kruskal-Wallis) nor magnitude of turning ($p=0.57$, Mardia-Watson-Wheeler) varied with stimulus location. Interestingly, turning was bimodal; rats either failed to turn or turned ~180 degrees. Body movement lagged movement of the stimulated tail or foot by only 58 to 130 ms and the time lag was similar for short (~1 s) and long (~8 s) latency responses, consistent with a common motor program. Variability in turning arose from a significant ($p<0.001$, Mardia-Watson-Wheeler) difference in rats; 4 failed to turn while two primarily turned, suggesting that different rats utilize different escape strategies. Our results suggest that studying the NWR in restrained rats may miss critical elements of the animal's escape strategy.

Disclosures: S. Mavi: None. **M.E. Pegelow:** None. **D.A. Grigoryan:** None. **C.L. Cleland:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.10/KK27

Topic: E.06. Posture and Gait

Title: Contributions of intrinsic tail muscles to the nociceptive withdrawal response in the rat

Authors: *H. IZADPANAH, C. L. CLELAND
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Noxious stimuli can evoke the nociceptive withdrawal response (NWR), which protects the affected part of the body. The tail, because of the large number of joint and muscle degrees of freedom, may present a computational challenge to the central nervous system. Previous studies have revealed that synergies act to reduce the number of degrees of freedom,

however there is little information in mammals on synergist control of hyper-redundant body parts, such as the tail of the rat. The long-term specific aim of this project is to test the hypothesis that during the NWR muscle synergies controlling rat's tail reduce the muscular degrees of freedom by recording the electromyogram (EMG) from intrinsic tail muscles during heat evoked NWRs. Adult, male Sprague Dawley rats were briefly anesthetized (isoflurane). The tail was marked in thirteen equally spaced locations along the dorsal surface of the tail for stimulation and tracking. To monopolarly record EMG, nine stainless-steel wires (0.002", Teflon insulated, 7 strands, de-insulated for 2 mm) were inserted subcutaneously with 25 gauge, 5/8" needles. Seven wires were inserted at seven adjacent marks, one was placed in the distal tail, which lacks muscle, to serve as a reference and a ground was placed in the proximal tail. Heat stimuli (980 nm infrared laser diode) were delivered to the lateral surface at 12 marked locations to evoke a NWR that was captured by high speed video (650 fps). EMG was conventionally amplified and filtered. Robust single and multi-unit EMG recording were obtained in two preliminary experiments. EMG was highly modulated by behavior, typically tonically active at rest and increased significantly during tail movement; in some instances EMG became quiescent. In response to heat stimuli and associated with the NWR, EMG was briefly activated followed by a variable period of silence. These results demonstrate that intrinsic tail muscles may contribute phasically to the NWR.

Disclosures: H. Izadpanah: None. **C.L. Cleland:** None.

Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.11/KK28

Topic: E.06. Posture and Gait

Support: NIH HD32571

Title: Behavioral adaptations during downslope walking after cross-reinnervation of medial gastrocnemius and the pretibial flexors

Authors: *M. A. LYLE[1], E. KAJTAZ[2], H. ANDERSON[2], H. SHI[2], B. RAPSAS[2], H. MAAS[3], T. NICHOLS[1]
[1]Dept. of Biol. Sci., [2]Georgia Inst. of Technol., Atlanta, GA; [3]VU Univ., Amsterdam, Netherlands

Abstract: Surgical cross-union of antagonist muscle nerves in the cat hindlimb results in activation patterns during locomotion that are mostly opposite their usual timing (e.g. extensor muscle active during swing) (e.g. Gordon, Stein and Thomas 1986). This scenario creates a mismatch between the muscle activation and mechanical activation of length and force

dependent sensory receptors. We hypothesize that this mismatch could be a stimulus for central reorganization of intermuscular spinal reflex circuitry, despite an apparent lack of central reorganization of pattern generator networks acting on native motoneuron pools. While motor activation patterns have been characterized after muscle nerve cross-unions, movement patterns have not been reported and whether spinal reflex circuitry reorganizes is unknown. Here, we report preliminary behavioral adaptations during downslope walking from 3 cats before and 8-9 weeks after cross-union of the nerve to medial gastrocnemius and deep peroneal nerve to the pretibial flexors. The most consistent adaptations after cross-union were during the stance to swing transition characterized by increased ankle extension in 2 cats and increased MTP extension in all cats through midswing, along with a tendency for increased knee flexion. An additional observation was increased ankle flexion during the stance phase after cross-union. The behavioral changes during swing could be explained by activation of the medial gastrocnemius by the pretibial flexor motor pool, and increased ankle flexion during stance could be explained by activation of the pretibial flexors and lack of medial gastrocnemius excitatory length feedback onto its motoneuron pool. The behavioral adaptations will be further investigated by recording EMG during locomotion, and terminal experiments will examine intermuscular length and force dependent spinal reflex circuitry. The findings from this work is anticipated to further our understanding of spinal plasticity and provide insight regarding functional outcomes after nerve transfer surgeries intended to restore function in patients.

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Poster

154. Reflexes and Reflex Modulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 154.12/KK29

Topic: E.06. Posture and Gait

Support: University of Nevada Las Vegas, Department of Physical Therapy (UNLVPT) Student Opportunity Research Grant

Title: Neuromuscular adaptations following acute bout of slope walking in individuals post-stroke

Authors: ***J. LIANG**[1], *J. LIANG[1], E. AKOOPIE[1], B. CONWAY[1], T. KOCH[1], Y.-J. LEE[2]
[1]Dept. of Physical Therapy, Univ. of Nevada Las Vegas, Las Vegas, NV; [2]Dept. of Industrial Engin. and Engin. Mgmt., Natl. Tshing-Hua Univ., Hsinchu, Taiwan

Abstract: *Background.* Excitability of the H-reflex pathway in non-impaired nervous systems can be augmented by altering the different parameters of a walking task, specifically slope. We

sought to examine the adaptations in soleus H-reflex excitability and foot force control following an acute bout of upslope or downslope treadmill walking in people post-stroke. *Methods.* 6 individuals with chronic post stroke hemiparesis and 3 age-similar non-neurologically impaired individuals were recruited. Each participant was tested over 2 sessions separated by at least 7 days. For each session, participants walked at self selected walking speed on an instrumented treadmill for 20 minutes under a level and then an upslope condition, or a level and then a downslope condition, with at least 1 hour rest inbetween the conditions. The vertical component of ground reaction forces was used to determine the stance and swing phases of the gait cycle. Peak propulsion and braking forces were analyzed for the first and last minute of each condition to examine foot force control. Soleus H-reflexes in the paretic legs of the stroke group and the right legs of the control group were tested before and after each walking condition. To ensure consistency, a control M wave preceding the H was kept constant across all conditions for each participant. Peak to peak amplitudes of the maximal H-reflexes and maximal M waves were measured offline and expressed as H_{max}/M_{max} ratios. *Results.* For both stroke and controls, peak propulsion forces during level walking were lower compared to upslope and greater compared to downslope. On the contrary, peak braking forces during level walking were greater compared to upslope and lower compared to downslope. In addition, peak propulsion and braking were greater in controls than in stroke for both legs, except for braking forces in the paretic legs. Following 20 minutes of level and downslope walking we observed increased propulsive forces in the paretic legs only and reduced H_{max}/M_{max} ratios in both control and paretic legs. Following upslope walking, we observed lower H_{max}/M_{max} ratio in controls but higher H_{max}/M_{max} ratios in paretic legs post stroke. *Conclusion.* Our results suggest that when the biomechanics of the walking task is altered, through adjusting the slope of the walking surface, paretic legs exhibit intact foot force control for propulsion but not for braking forces. In the level and downslope condition, spinal circuits in the stroke-impaired nervous system undergo adaptations similar to the non-impaired nervous system. However, in the more challenging upslope condition, adaptations of the paretic soleus H-reflexes were impaired.

Disclosures: **J. Liang:** None. **E. Akoopie:** None. **B. Conway:** None. **T. Koch:** None. **Y. Lee:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.01/KK30

Topic: F.01. Neuroethology

Support: NSF Grant 1257923

Title: Controlling from behind the scenes - Tritonia swim CPG neuron C2 paradoxically drives crawling while silent

Authors: *E. S. HILL, J. WANG, W. N. FROST
Cell Biol. and Anat., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL

Abstract: The escape swim central pattern generator (CPG) of the marine mollusk *Tritonia* represents a striking example of a multifunctional network. First, its DSI, C2 and VSI neurons generate the rhythm that drives the animal's muscle-mediated escape swim. Following that, the DSI neurons continue firing tonically for up to an hour to drive crawling, a non-rhythmic behavior mediated by cilia on the animal's foot. Do the other members of the swim CPG also participate in driving these two very different behaviors? Here we show that CPG neuron C2 does so, but surprisingly while remaining silent during the post-swim crawling period.

In isolated brain preparations, C2 fires vigorously and rhythmically during the swim motor program (SMP). Following the motor program C2 immediately stops firing and remains silent during the entire post-swim crawling period, giving the impression that it does not participate in driving crawling. However, in these deafferented preparations the possibility of feedback from the periphery has been eliminated. Thus we obtained intracellular recordings from C2 in intact animal preparations undergoing tethered escape swims, with peripheral feedback fully present, and confirmed that C2 similarly returned to silence immediately following the SMP, consistent with its having no role in driving crawling.

We were therefore surprised to find that in semi-intact preparations, where head-to-tail movement of carbon particles sprinkled on the foot can be used as a monitor of crawling, directly driving C2 produces a strong and paradoxical activation of locomotion cilia that only occurs once C2 stops firing. In fact, this off-response stimulatory action by C2 on foot cilia is considerably stronger than that produced by directly driving any of the previously identified cilia-activating neurons (DSI, Pd21, Pd5, Pd6). We speculate that this post-burst stimulatory effect by C2 on the foot cilia may contribute importantly to the crawling that begins upon swim cessation.

Given that C2 is known to produce delayed excitation of some pedal ganglion swim flexion neurons, we hypothesized that it may produce similar delayed excitation of a previously unknown population of cilia-activating neurons in the pedal ganglion. Using voltage-sensitive dye imaging, we found that many pedal ganglion neurons fire at an elevated tonic rate during the post-swim motor program crawling period, and that directly driving C2 elicits tonic firing of up to 20 dorsal pedal ganglion neurons for tens of seconds. Taken together, our data reveal an unsuspected, potent and paradoxical role for C2 in crawling, and demonstrate that neurons need not be actively firing to strongly influence behavior.

Disclosures: E.S. Hill: None. **J. Wang:** None. **W.N. Frost:** None.

Poster

155. Motor Systems: Neuromodulation

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Program#/Poster#: 155.02/KK31

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF Grant IOS-1455527

March of Dimes Foundation Grant 6-FY14-441.

Title: Single neuron RNA-seq and qPCR show correlation of 5-HT receptor subtype expression with species and individual differences in sea slug swimming behaviors

Authors: *A. N. TAMVACAKIS, P. S. KATZ
Georgia State Univ., Atlanta, GA

Abstract: Neuromodulators, such as serotonin (5-HT), act on G-protein coupled receptors (GPCRs) to alter synaptic and membrane properties of neurons. Species differences in GPCR expression by homologous neurons could be a mechanism underlying species differences in behavior. In the nudibranch, *Tritonia diomedea* (Mollusca, Gastropoda), 5-HT plays a crucial role in dorsal-ventral (DV) escape swimming by modulating the synaptic strength of a swim central pattern generator (CPG) neuron called C2. The nudibranch *Hermissenda crassicornis* is not a DV swimmer; nevertheless a C2 homolog and 5-HT are present. However, C2 synaptic strength is not modulated by 5-HT. *Pleurobranchaea californica*, a sister species to the nudibranchs, performs an analogous DV swimming behavior, which evolved independently from that of *Tritonia*. However, individual *Pleurobranchaea* exhibit daily variability in whether they swim. In *Pleurobranchaea*, the C2 homolog is a member of its swim CPG, and 5-HT modulates C2 synaptic strength. However, the extent of that modulation correlates with swimming on the day of testing. Here, we examine 5-HT receptor subtype expression in C2 homologues and correlate it with swimming within and between species.
Seven 5-HT receptor subtype genes were identified in whole-brain tissue. To determine which receptors were expressed by C2 in each species, we isolated individual C2 neurons and performed both single neuron RNA sequencing and quantitative PCR (qPCR). We found that C2 neurons isolated from *Tritonia* and swimming *Pleurobranchaea* brains expressed 5-HT receptor subtypes known as 5-HT2a and 5-HT7. These subtypes were absent from C2 homologues isolated from *Hermissenda* and non-swimming *Pleurobranchaea*. Within the single-cell transcriptomes, we also found several other receptors, although none correlated with swimming. The correlation between swimming and specific 5-HT receptor subtypes indicates that these receptors may mediate the modulation of C2 synaptic strength and thus play an important role in DV swimming. Furthermore, the results suggest that species and even individual differences in GPCR expression may underlie differences in behavior.

Disclosures: A.N. Tamvacakis: None. **P.S. Katz:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.03/KK32

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Peptide profiles of key regulatory interneurons in the sea slug Pleurobranchaea californica

Authors: *C. LEE[1], E. ROMANOVA[2], J. BOYKIN[3], A. N. TAMVACAKIS[3], P. S. KATZ[3], R. GILLETTE[4], J. V. SWEEDLER[2]
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Abstract: Although the decision-making and pattern generating circuits of several gastropods have been described, roles of their signaling peptide neurotransmitters are less understood. How prevalent is peptide signaling and how important is it to the functioning of the neural circuits? To answer these questions, we are identifying peptides present in key interneurons of feeding and turn-locomotion-swim (TLS) networks of the nudipleuran *Pleurobranchaea californica*. Using mass spectrometry, we characterized peptide profiles of three such interneurons: the A1 cell (an element of the TLS necessary for the escape swim and inhibition of feeding), the ventral white cell, (VWC; a feeding command cell), and the feeding network efference copy cell (a neuron providing efference copy of feeding activity to the stomach). Each neuron is intensely white and easily visually identifiable. Previous immunostaining studies labelled the A1 cell for FMRFamide and SCP_B (Lillvis *et al*., 2012). We found peptides from prohormones homologous to *Biomphalaria* (35% homology) FMRFamide and FMRFamide-like (38%) prohormones, but did not find any peptides from the SCP_B prohormone. Additionally, we found peptides from prohormones homologous to those for *Aplysia* pedal peptide 3 (50%) and 4 (48%). Surprisingly the VWC contained peptides from the same prohormones as the ones in the A1 cell, and also contained SCP_B. Finally, the efference copy cell only contained peptides from a prohormone homologous to the *Lymnaea* LFRFamide prohormone (43%). In addition, we obtained preliminary evidence suggesting that the serotonergic metacerebral cells, which provide excitatory neuromodulatory input to the feeding network, also contain peptides. It will be of interest to ascertain the roles of the peptides in sensory-motor integration and behavioral choice among feeding and TLS behaviors in *Pleurobranchaea*.

Disclosures: C. Lee: None. **E. Romanova:** None. **J. Boykin:** None. **A.N. Tamvacakis:** None. **P.S. Katz:** None. **R. Gillette:** None. **J.V. Sweedler:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

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Program#/Poster#: 155.04/KK33

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R01 NS066587

NIH Grant R01 MH051393

NIH Grant R01 NS070583

Title: Neural plasticity supporting repetition priming is maintained by a persistent elevation of cAMP

Authors: *M. H. PERKINS[1], E. C. CROPPER[2], K. R. WEISS[2]
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Abstract: In free moving Aplysia, feeding responses are primed when they are repeatedly elicited. An important component of priming is an increase in the magnitude of radula opening. To determine how this priming is mediated we conduct experiments that take advantage of the fact that fictive feeding motor programs can be induced in vitro by stimulating a command-like neuron, CBI-2. When CBI2 is repeatedly stimulated to produce a series of motor programs, the firing of the radula opener neuron B48 increases, i.e., it shows priming. Priming of B48 involves an increase in B48 excitability, and the effects of priming are persistent. B48 motor program activity and excitability remain elevated in programs for more than thirty minutes after repeated CBI-2 stimulation ends. What could account for the persistent excitability increase observed with priming? We measured a persistent inward current that has a time course similar to the increased excitability observed with priming. Induction of this current by CBI-2 priming depends on cAMP signaling, as it is blocked by Rp-cAMP, which also blocks priming of B48 motor program activity and excitability (Friedman 2012). What maintains this persistent inward current? As the inward current's induction depends on cAMP, we reasoned that its persistence would depend on PKA, as this is the canonical way cAMP affects cell physiology over longer time scales. Blocking PKA activity by loading B48 with a specific peptide inhibitor, PKI, did not reduce the persistent inward current or the increase in excitability. This raises the possibility that cAMP itself is required for the maintenance of B48 priming. The maintenance of the persistent inward current in B48 is disrupted by delayed loading of Rp-cAMP, after establishing the current by priming B48. These experiments suggest that a form of neural plasticity that lasts for more than thirty minutes is maintained by a persistent elevation in cAMP.

Disclosures: M.H. Perkins: None. **E.C. Cropper:** None. **K.R. Weiss:** None.

Poster

155. Motor Systems: Neuromodulation

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Program#/Poster#: 155.05/KK34

Topic: B.07. Synaptic Transmission

Support: NIH MH060605

NIH NS083319

Title: Different neuromodulators directly influence gap junction-mediated electrical coupling strength in oscillatory networks

Authors: *X. LI, D. BUCHER, F. NADIM
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Abstract: Electrical synaptic coupling through gap junctions is ubiquitous in vertebrate and invertebrate nervous systems. Electrical coupling influences network activity by interacting with other network components, including chemical synapses and voltage-gated ionic currents. Both experimental and theoretical studies have demonstrated critical roles for electrical synapses in rhythmogenesis, synchronization and pattern formation in various networks. The role of electrical coupling in network oscillations, in particular, has been the subject of numerous theoretical studies and, more recently, demonstrated in a number of brain rhythms.
Like all network components, electrical coupling is subject to neuromodulation. Yet, the mechanisms underlying neuromodulation of electrical coupling and its functional impact on the network are mostly not well understood. Modulators can affect electrical coupling indirectly by targeting synaptic and voltage-gated ionic currents which influence the coupling coefficient. However, due to technical difficulties, few studies have explored the direct neuromodulation of individual electrical connections. To understand how network activity is shaped by neuromodulators, it is important to first examine the direct influence of neuromodulators on electrical synapses, independent of other network components.
We examine this problem in neurons of the stomatogastric ganglion (STG) of the crab *C. borealis.* We studied the effect of two modulatory neuropeptides: proctolin and crustacean cardioactive peptide (CCAP) on the electrical coupling between the two pyloric dilator (PD) neurons. The two PD neurons are members of the pacemaker group of the oscillatory pyloric network. Neurons in this pacemaker group are strongly electrically coupled and always oscillate in synchrony. We measured the bi-directional coupling current between these neurons with dual two-electrode voltage clamp when they are synaptically isolated from the network. Our results show that proctolin reduces the coupling conductance, while CCAP increases it. We are currently exploring the effect of a number of other neuromodulators on this coupling conductance and examining other STG electrical synapses.

To study the functional effect of the neuromodulation of electrical coupling, we will examine whether the degree of synchrony in slow-wave oscillations or spike timing between the two PD neurons is altered in the presence of neuromodulators. Together, these results would provide strong evidence for direct neuromodulation of electrical synapses and its functional effect at the network level.

Disclosures: X. Li: None. **D. Bucher:** None. **F. Nadim:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.06/KK35

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF grants IOS-1353023 and IOS-1354567

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UHManoa's Undergrad Res. Opp. Prog.

Title: Differential bioactivity of mature and partially processed forms of a neuromodulator, myosuppressin, on the cardiac neuromuscular system of the American lobster, Homarus americanus

Authors: *M. STANHOPE[1], T. X. DIAZ[1], M. G. PASCUAL[2], A. YU[2], A. E. CHRISTIE[2], P. S. DICKINSON[1]
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Abstract: Peptides are one of the largest classes of signaling molecules, and are imperative for communication and flexibility within neuronal systems. The cardiac neuromuscular system of the American lobster, *Homarus americanus*, serves as a useful model for understanding the mechanisms by which these peptides exert their effects. Myosuppressin (pQDLDHVFLRFamide), a relatively well-characterized peptide modulator of the cardiac neuromuscular system, has been shown to act centrally on the cardiac ganglion (CG) to cause a decrease in contraction frequency. It also acts peripherally on either the muscle or neuromuscular junction to elicit a slightly delayed increase in contraction amplitude. In this study, we investigated the role of the two post-translational modifications of the peptide: the cyclization of

the (N)-terminal glutamine and the (C)-terminal amidation. Analysis of a transcriptome from the CG suggests that the enzymes required for these post-translational modifications are present in the cardiac ganglion. Thus, we tested the effects of three peptides, representing fully and partially processed myosuppressin, on the cardiac neuromuscular system. In whole heart preparations, both mature myosuppressin and non-cyclized myosuppressin (10^{-6} M) caused a significant decrease in contraction frequency and a slight decrease in contraction amplitude followed by a delayed increase in amplitude. The non-amidated peptide (10^{-6} M), however, elicited a decrease in contraction frequency, but only a decrease in contraction amplitude. Bioinformatic analyses suggest the possibility that more than one myosuppressin receptor variant is present in the CG, and that a receptor variant may also exist in the cardiac muscle (CM). If it is confirmed, such differential distribution of myosuppressin receptors in the CG relative to the CM suggests at least one hypothesis to explain these data. Specifically, if multiple isoforms of the myosuppressin receptor are present in the CG, the CG may be able to respond to different isoforms of myosuppressin, including those that lack post-translational modifications. In contrast, the muscle may only express one isoform of the myosuppressin receptor, which might be more selective, with certain isoforms, such as those lacking the (C)-terminal amidation, failing to bind at this site.

Disclosures: M. Stanhope: None. **T.X. Diaz:** None. **M.G. Pascual:** None. **A. Yu:** None. **A.E. Christie:** None. **P.S. Dickinson:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.07/KK36

Topic: E.07. Rhythmic Motor Pattern Generation

Support: The Israel Science Foundation (ISF) 1591/08, 1930/08, 491/12, and 1833/16

Title: Sacral networks shape the output of lumbar motoneurons by direct rostral projections of relay neurons through the ventral funiculus

Authors: M. CHERNIAK[1], L. ANGLISTER[2], *A. LEV-TOV[2]
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Abstract: Spinal central pattern generators produce the rhythmic neural output required for coordinated and stabilized locomotion by activating the limb, trunk, and axial musculature. Previously we showed that sacrocaudal networks that control the axial and tail musculature of the neonatal rat activate and modulate the limb-moving lumbar networks in the absence of supraspinal control. Using confocal microscopy mapping, trans-synaptic retrograde labeling with

GFP-encoded viral vectors, surgical manipulations, electrophysiological recordings and calcium imaging, we describe direct mono/oligo synaptic pathway between ventral groups of sacral relay neurons (vSRNs) and rostral lumbar motoneurons. Activation of sub-group of vSRNs with rostral projections through the ventral white matter funiculi by alpha-1 adrenoceptor agonist and sacral afferents increases the excitability of rostral lumbar motoneurons thereby shaping the motor output during motor behaviors. Possible clinical uses of the capacity of drug/electrical stimulation to improve the motor function will be discussed.

Disclosures: M. Cherniak: None. **L. Anglister:** None. **A. Lev-Tov:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.08/LL1

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Modulation of myogenic contractions in the ventral diaphragm muscle in Manduca sexta reveals a mixed excitatory and inhibitory response to glutamate

Authors: E. T. REIS, V. P. HALULA, *R. J. BAYLINE
Washington and Jefferson Coll, Washington, PA

Abstract: Myogenic muscles in both insects and vertebrates control circulation. In *Drosophila melanogaster* and *Manduca sexta,* a myogenic heart operates in the adult moth to circulate hemolymph. In the moth *Manduca sexta*, the ventral diaphragm muscle (VDM) shares properties with the dorsal heart muscle and acts as an accessory circulatory muscle. Neuronal activity modulates the activity of both the VDM and dorsal heart. The dorsal heart shows a differential response to neural stimulation depending upon which region of the heart is stimulated. We hypothesize that the VDM will show excitation from neurotransmitters known to excite the dorsal heart muscle due to the similarities between the VDM and dorsal heart. We anticipate that the response of the VDM may differ in anterior, middle, and posterior regions. Similar to the dorsal heart the VDM receives innervation in both the anterior (A2-A3) and posterior (A6) segments. The central segments (A4-A5) receive no innervation. Bath application of the neurotransmitter glutamate (10^{-6} M), which is excitatory on the dorsal heart, is expected to enhance the contractile rate and strength of VDM activity. When glutamate was added to the intact VDM a 14.2% increase in oscillation rate was recorded, indicating excitatory effects of glutamate. Conversely, a decrease in oscillation rate of 27.7% was recorded when glutamate was added to the isolated segments A4-A5. This suggests that the VDM may have multiple types of glutamate receptors. In the posterior segments, we propose that excitatory glutamate receptors mediate the enhancement of activity observed when glutamate is bath applied to the entire VDM. When the uninnervated A4-A5 segments are isolated, inhibitory action of glutamate is mediated

by a different set of receptors. This suggests that the effects of glutamate upon the VDM during normal circulatory function may depend upon the localization of glutamate release upon the VDM.

Disclosures: E.T. Reis: None. **V.P. Halula:** None. **R.J. Bayline:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.09/DP07/LL2 (Dynamic Poster)

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH Grant 5R01NS026539-28

Title: Activity patterns of age-labeled Chx10 interneurons during whole-brain imaging

Authors: *D. M. CHOW, J. R. FETCHO
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Abstract: Neuronal diversity plays an important role in the logic and construction of neural circuits. Even within a neuronal subtype defined by a single transcription factor, such as Chx10, there exists variation in physiological properties, functional role, and anatomical positioning that may tailor the neurons to their particular networks. In larval zebrafish, a topographical gradient of neuronal age and physiological properties link motor recruitment to dorsal-ventral position within transcription-factor labeled hindbrain stripes. Some neurons within the Chx10 transcription factor stripe exhibit a gradient of morphology, input resistance, and recruitment in swimming. Younger, dorsal neurons are recruited at slow swim frequencies while older, more ventral neurons are recruited during more powerful swimming and escapes. However, the functional significance of such organization, its presence in other networks, and its spatial extent remains poorly studied. We have performed whole-brain calcium imaging utilizing light sheet microscopy on 4-6 d.p.f. zebrafish larvae co-expressing Chx10-Kaede and pan-neuronal nuclear-localized GCamP6S/F in order to examine the activity patterns of age-labeled Chx10 neurons on a broad scale. Simultaneously, we monitored ventral-root activity and delivered electrical tail shocks to evoke motor behaviors. Conversion of Chx10-kaede from its green to red form at 30 hours post-fertilization allowed identification of older versus younger neurons prior to calcium imaging. Both stimulus-related and motor-related neuronal populations were identified on a brain-wide scale. Clustering analysis of Chx10 neurons reveals both lateralized, region-specific populations of cells, and also more widely-dispersed populations of neurons. Our preliminary data indicates that under evoked conditions driving strong motor output both young and old neurons in widely dispersed clusters exhibited similar patterns of activity. Furthermore, more localized clusters only contained young Chx10 neurons. Simultaneous broad-scale imaging and

analysis of stimulus and motor-related activity patterns across large swaths of the nervous system will help us to understand the diversity of function present within this transcription-factor labeled neuronal group and shed insight into functional organization related to neuronal age across the brain.

Disclosures: D.M. Chow: None. **J.R. Fetcho:** None.

Poster

155. Motor Systems: Neuromodulation

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 155.10/LL3

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR MOP-130528; PJT-148682

NSERC RGPIN/356153-2013

Title: Complex dopamine receptor interactions exert diverse modulation on spinal networks of the neonatal mouse

Authors: *S. A. SHARPLES[1], N. E. BURMA[3], H. L. LEDUC-PESSAH[3], C. JEAN-XAVIER[2], P. J. WHELAN[4]
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Abstract: Monoamines modulate rhythmic networks of the lumbar spinal cord. We have previously shown that modulation is dependent on excitability state and that dopamine exerts more diverse effects during a low excitation state than at a high excitation state. Here we show that in a low excitation state that low concentrations of dopamine are inhibitory, whereas high concentrations are excitatory. Therefore, we sought to determine the receptor mechanisms that underlie this bi-directional modulation.
As predicted, low concentrations (1-30 µM) of dopamine inhibited the network by acting in parallel on D_2, D_3 and D_4 receptors. A portion of this inhibitory effect was due to cross-reactivity of dopamine with alpha-2 adrenergic receptors. Increasing the endogenous levels of dopamine by blocking the dopamine transporter recapitulated this inhibitory effect.
Higher concentrations of dopamine (>30 µM) excite the network by not only by acting on D_1-like receptors, but also by co-activating D_1 and D_2 receptors as blocking D_1 or D_2-like receptors attenuates the excitatory effect. In line with this, co-application of a D_1- agonist with a D_2-agonist or a co-agonist exerted more robust excitation of the network compared to a D_1-agonist alone. Using co-immunoprecipitation we assessed the interaction between D_1 and D_2 receptors.

Parallel activation of inhibitory dopamine receptors and alpha-2 adrenergic receptors maintain network quiescence in the presence of low concentrations of dopamine (particularly those present endogenously). As exogenous dopamine concentration increases, activation of both D_1 and co-activation of D_1-D_2 receptors elicit robust excitation of the network. While the excitatory D_1 receptor system is functional and may cross-activate with D_2 receptors, our prediction is that during development dopamine acts as a "brake" on spontaneous activity to prevent excessive activation of the network.

Disclosures: S.A. Sharples: None. **N.E. Burma:** None. **H.L. Leduc-Pessah:** None. **C. Jean-xavier:** None. **P.J. Whelan:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.01/LL4

Topic: F.01. Neuroethology

Support: JSPS KAKENHI 15J02077 to MS

JSPS KAKENHI 16H06544 to HO

Title: Coincident multisensory inputs enhance bursting activity via large and long-lasting EPSPs in insect auditory neuron

Authors: *M. SOMEYA[1], H. OGAWA[2]
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Abstract: Animals, including insects, integrate multiple modalities of sensory inputs for accurate perception of surrounding environment. For example, early detection of a predator is crucial for successful escape and is improved by multisensory integration of several signs of the approaching predator. Understanding the neural mechanisms of multisensory integration improving the predator detection is one of the most important themes in neuroethology. To address this question, we focused on the auditory and cercal sensory systems of crickets, both of which mediate the predator's signs. In the auditory system, a pair of identified ascending projection neurons, called AN2, respond to ultrasound for echolocation of bat and their bursting activity elicits avoidance behavior during the flight. In the cercal sensory system, several mechanosensory projection neurons identified as giant interneurons (GIs) represent the general parameters of air currents such as direction and dynamics. Excitation of some GIs triggers the escape behaviors in which crickets walk away from the stimulus source. Both of ultrasound and airflow are perceived as signals of predator's attack, but the multisensory integration between

auditory and cercal sensory systems and behavioral impacts of these cross-modal cues remain unclear. In the present study, we found that AN2 responded not only to ultrasound but also to airflow. When the sound and airflow stimuli were applied to the cricket simultaneously, AN2 generated burst firing that was larger response than the linear summation of individual responses to sound and airflow. The EPSPs evoked by the combined stimulus were larger and longer lasting than those evoked by sound or airflow stimulus only. In addition, we also found that the threshold of the second or later spike was elevated as inter-spike interval (ISI) became shorter. Previous study reported that AN2 conveys echolocation information in the structure of their burst firing. Our result suggests that the spike-threshold elevation depending on the ISI suppresses frequent burst firing in response to the mono-modal stimulus, which may underpin the accurate detection of the echolocation. The multisensory inputs evoked large and long-lasting EPSP that enable to generate the burst firing against dynamic spike threshold elevation. This multisensory integration mechanism in AN2 would play an important role in the early and accurate detection of bats.

Disclosures: **M. Someya:** 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.; JSPS KAKENHI 15J02077, JSPS KAKENHI 16H06544. **H. Ogawa:** 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.; JSPS KAKENHI 15J02077, JSPS KAKENHI 16H06544.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.02/LL5

Topic: F.01. Neuroethology

Support: MEXT KAKENHI 16H06544

Title: Crickets modulate wind-elicited escape behavior depending on auditory context with sound carrier frequency

Authors: *M. FUKUTOMI[1], H. OGAWA[2]
[1]Grad. Sch. of Life Sci., [2]Dept. of Biol. Sciences, Fac. of Sci., Hokkaido Univ., Sapporo, Japan

Abstract: Animals receive specific auditory cues and exhibit distinct behaviors depending on the acoustic information. Insects display various acoustic behaviors such as approaching to a mating partner and avoidance from a predator. These behaviors are considered as 'stereotyped' reactions

which are triggered by a specific releasing stimulus. It had been unknown whether the general acoustic sound triggering no reactions by itself can modulate insects' behaviors elicited by other modality of sensory stimulus. Recently, we have reported that a preceding auditory stimulus (10-kHz pure tone) that solely evoked no response modulated directionality and response threshold in wind-elicited walking behavior of the cricket (Fukutomi et al., 2015). It revealed that a cross-modal interaction between auditory and mechanosensory (cercal) systems induced the behavioral modulation, suggesting that crickets can alter their escape strategies depending on the acoustic context. The carrier frequency of sound is a major factor of the acoustic contexts for crickets. Low-frequency sound (~5 kHz) which corresponds to the carrier frequency of conspecific calling song and induces positive taxis in the cricket. In contrast, the flying crickets display avoidance behavior in response to high-frequency sound, which will be detected as foraging bats' echolocation calls (>10 kHz) (Popov and Shuvalov, 1977). Does the auditory modulation of the wind-elicited behavior depend on the acoustic contexts expressed by different carrier frequencies? To address this question, we measured walking trajectories of the escape responses to air-puff, and compared the cross-modal effects between low-frequency (5 kHz) and high-frequency (15 kHz) tones. Both pure tones elicit no walking reactions, but the impact on the escape response was different between high- and low-frequency of sounds. The high-frequency tone decreased response probability like 10-kHz tone in the previous work, but low-frequency tone had no effect. Similar to the previous study, both frequencies of sounds promoted backward walking in response to the air puffs from lateral or frontal air-puff. However, the backward bias induced by the high frequency tone was larger in angular magnitude than that by low frequency tone. These differences in the behavioral modulation between the sound frequencies suggest that crickets can adapt their escape strategy depending on the acoustic contexts. Collectively, we suppose the possibility that insect auditory system is used not only for detecting a specific feature to trigger the stereotyped behavior but also for perceiving the acoustic context for decision making.

Disclosures: **M. Fukutomi:** None. **H. Ogawa:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.03/LL6

Topic: F.01. Neuroethology

Support: MEXT KAKENHI 16H06544

Title: Action selection between walking and jump in the wind-elicited escape behavior of the cricket

Authors: *N. SATO[1], H. OGAWA[2]
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Abstract: Animals exhibit various behaviors appropriate to the occasion in environment. Especially, which reaction to select against the predator is critical for the animal to survive. Facing the predator, the animals adopt various reactions for survival, however the neural basis on the action selection of 'how to escape' remains unknown. A field cricket, *Gryllus bimaculatus*, detects airflow stimulus as predator's approach by the cercal sensory system and exhibits some different behaviors including escape (Baba and Shimozawa, 1997). As the escape behavior elicited by the airflow, crickets display two distinct actions, running and jump, suggesting that the crickets make decisions for the action selection between running and jump for successful escape. The crickets are, therefore, potentially capable of a good model organism to investigate the neural mechanism for decision making of the action selection. In this study, we firstly focused on the stimulus parameters that have impacts on the action selection in the wind-elicited escape behavior. Previous study reported that faster air-current elicited the escape behavior more frequently (Baba and Shimozawa, 1997). And, crickets are likely to turn before jump in response to the airflow applied from front or lateral side (Tauber and Camhi, 1995). To determine the relationship between the selected action and the velocity or direction of the stimulus, we examined the dependency of the action selection for the wind-elicited escape on the velocity and the arrival angle of the airflow. The jump response was selected more frequently as the airflow speed increased. And, the airflow applied from behind elicited the jump more frequently than that from other angles. These results suggest that the cricket make choice of the escape reactions depending on the stimulus intensity and angle. Next, we hypothesized that the crickets choose the escape action depending on 'trade-off' between the reaction speed and directional accuracy; crickets may jump to escape more quickly and farther away, while they may select running to distance themselves effectively from the approaching predator. To test this hypothesis, we examined the difference between running and jump in the motor performance, and estimated the adaptive significance of this action selection. The travel distance and maximum velocity in jump reaction were larger than those in running reaction. In contrast, there was no significant difference in the reaction time and the accuracy of directional control between running and jump. These results mean that this action selection is not simply based on the trade-off between reaction speed and directional accuracy.

Disclosures: N. Sato: None. **H. Ogawa:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Program#/Poster#: 156.04/LL7

Topic: F.01. Neuroethology

Support: MU Undergraduate Research Award

Biology Department

Title: Cold temperature stress increases gut permeability and leads to changes in behavior

Authors: K. KOHL[1], H. M. CHARLES[1], A. UNGER[1], K. SCHULTZ[1], *K. A. KILLIAN[2]
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Abstract: Loss of gut barrier integrity has been linked to changes in nervous system function and behavior. Here, we report that exposing male *Acheta domesticus* crickets to 0°C cold stress (CS) increases gut permeability and negatively impacts social behavior. We used a dye permeability assay to demonstrate changes in gut integrity following CS. Adult male crickets were provided with 2.5% FD&C Blue Dye #1 in drinking water for 2d and were then subjected to 0°C CS for 1h or 6h. When examined 1-3 h post-CS, significantly more 6h CS males (25/29; $p<0.0001$) and 1h CS males (3/20; $p=0.02$) had blue dye outside the gut compared to non-cold stressed (NCS) males (0/29). These results support loss of intestinal barrier integrity following cold stress. There was no significant difference in the number of 6h CS males (2/17) and NCS males (3/14) with dye leakage 24h after CS ($p=0.47$), indicating barrier integrity is quickly restored. We also found significantly more nodules in abdomens of males that received a 1h or 6h CS compared to NCS males. As part of the innate immune response, hemocytes aggregate around foreign invaders and produce melanin to form a hardened nodule that isolates the invaders. Our nodulation data thus supports that loss of gut barrier integrity following CS allows bacteria to escape the gut, enter the hemocoel, and trigger systemic inflammation. We also examined the impact of CS on male cricket social behavior. For agonistic trials, a male that received either a 1h or a 6h CS was placed in an arena with a NCS male 7d post-CS. Significantly more males receiving 6h CS became socially subordinate in trials with NCS males ($n=32$ pairs; $p=0.002$), while 1h CS males were as likely to become dominant as NCS males ($n=33$ pairs; $p=0.08$). Also, trials of 6h CS and NCS males were just as aggressive as those of two NCS males ($n=32$; $p=0.34$), indicating that changes in male motivational state, rather than motor impairment, may lead to the reduced ability of 6h CS males to win a fight. CS also significantly impacted male mating behavior. For mating trials, a male cricket that received a 1h or 6h CS was paired with an age-matched female. Significantly fewer 6h CS males (2/29) successfully mated during the 10 min trials than did NCS males (16/32; $p<0.0002$), while 1h CS males (15/35) were just as successful as NCS males ($p=0.56$). Most 6h CS males failed to mate because they lacked a spermatophore, and not because of any visible motor impairment. In fact, chemosensory contact with a female could motivate many 6h CS males (12/13) to produce a spermatophore within 1h after contact. In conclusion, cold stress increases gut permeability, leading to bacterial escape, systemic inflammation, and lasting impact on male social behavior.

Disclosures: K. Kohl: None. **H.M. Charles:** None. **A. Unger:** None. **K. Schultz:** None. **K.A. Killian:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.05/LL8

Topic: F.01. Neuroethology

Title: Complex visual processing during action selection in *Drosophila melanogaster*

Authors: *H. JANG, B. W. MCFARLAND, L. J. SOLOMON, C. R. VON REYN
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Abstract: Action selection often requires sensory integration across both brain hemispheres. However, we know little about the neural circuits responsible for bilateral integration that drive behavioral responses to sensory stimuli. Here, we take advantage of neurogenetic tools, accessible neural circuits, and robust, easily quantifiable escape behaviors of the fruit fly *Drosophila melanogaster* to study neuronal pathways involved in bilateral sensorimotor transformations. In response to a looming stimulus, perched *D. melanogaster* perform takeoff escapes regardless of the stimulus being limited to a single eye or expanding across both eyes. Similarly, the giant fiber (GF) descending interneurons that drive escape respond to ipsilateral, contralateral, and bilateral stimulus presentations. Previous research identified visual projection neurons (lobula columnar neurons type 4, LC4) that convey ipsilateral angular velocity information to the GF circuit. The neurons that provide visual information from the contralateral hemisphere, however, remain unknown. In *D. melanogaster*, GFs dye couple to giant commissural interneurons (GCI/AMMC-A1) that arborize in the antennal mechanosensory and motor center (AMMC) and transmit mechanosensory information to the GF circuit. By using a MultiColor FlpOut (MCFO) technique, we support previous anatomical evidence that GCI dendrites arborize ipsilateral to their cell bodies within the posterior ventrolateral protocerebrum (PVLP) where LC4 axons terminate. Additionally, GCI axons project to the contralateral hemisphere and terminate in gorget (GOR) and PVLP regions adjacent to GF dendrites. GCI are therefore prime candidates for integrating and transmitting contralateral visual information to the GF circuit. To test functional connectivity between GF and GCI, we used optogenetics to activate GCI while recording GF responses using whole-cell patch-clamp in tethered, behaving flies. GCI activation resulted in significant GF depolarizations as compared to control flies (t-test, $p<<0.05$, $n=5$ flies) and evoked takeoff escapes in a subset of flies. We also found evidence for reciprocal excitation when activating GF and recording from GCI. These results suggest that GCI form functional synapses with GF and can mediate escape behavior. Future studies will investigate GCI visual sensory tuning and determine how GCI contribute to visually-evoked, GF-mediated escape behaviors. This work further establishes *D. melanogaster* escape behavior as an ideal model to investigate how neural circuits are interconnected, how they integrate sensory input, and how they guide action selection in response to sensory stimuli.

Disclosures: **H. Jang:** None. **B.W. McFarland:** None. **L.J. Solomon:** None. **C.R. von Reyn:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.06/LL9

Topic: F.01. Neuroethology

Title: A novel visual assay for escape behavior in *Drosophila*

Authors: *D. P. GOODMAN[1], A. ELDREDGE[1], M. KABRA[2], K. BRANSON[2], C. VON REYN[1]
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Abstract: The selection of appropriate behavioral output involves the integration of both internal states and external stimuli, but the neural substrates for action selection remain relatively unexplored. Escape behavior in the fruit fly, *Drosophila melanogaster,* provides an excellent model for examining action selection circuitry as *D. melanogaster* select between easily quantifiable motor programs in response to predation attempts and provide tractable neural complexity and a robust genetic toolkit that enable stimulation, silencing, and imaging of precisely targeted neural populations. In response to a single looming visual stimulus presentation, freely behaving flies respond with either a short or long duration takeoff escape sequence (‘short’ and ‘long’). It remains to be determined whether individual flies have an inherent bias in their response distribution and how this distribution changes over repetitive stimulation, since current free behavior escape assays are limited to single stimulus presentations per fly. Using a novel escape behavior assay that permits repetitive stimulus presentations, we here examined the distribution of escape responses in tethered flies under a range of experimental manipulations. In this assay, a looming stimulus (r/v = 40ms) projected on a cylindrical screen was presented to the central visual field of individual flies every 15 seconds for 20 trials. Behavioral responses were recorded at 1300 fps and classified both manually and with computer vision algorithms. We validated that the escape responses of tethered flies recapitulate the responses observed for freely behaving flies to identical stimuli in terms of absolute rate of takeoff escapes to initial stimulus presentations and the distribution between short and long duration responses. We also confirmed similar behavioral deficits when silencing key circuit elements required for takeoff escapes in freely behaving flies. For repetitive stimulus presentations, fly takeoff rates decreased by 25% between the first 3 and final 3 trials (χ^2 test of homogeneity, n=598, $p < 4.7x10^{-10}$). Within each fly, there was a significant amount of variation in escape performance, with 45% of subjects demonstrating escape ratios significantly different

from their population (χ^2 test of homogeneity, n=85, $p < 0.05$). Future work will utilize this assay for neurogenetic screens, where the tethered fly can be recovered for dissection. The presentation mechanism can also be easily adapted for more complex stimuli. In conclusion, our tethered, visually-evoked escape behavior assay provides a robust means of investigating action selection in a controlled and flexible visual environment.

Disclosures: D.P. Goodman: None. **A. Eldredge:** None. **M. Kabra:** None. **K. Branson:** None. **C. von Reyn:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: Arthur A. Haberberger Chairman's Endowed Student-Faculty Research Program

Lycoming College Professional Development Grant

Title: Genetic analysis of spontaneous grooming behavior in the fruit fly *Drosophila melanogaster*

Authors: C. L. HANNUM, *D. R. ANDREW
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Abstract: Grooming is an innate behavior with inherent fitness consequences in a wide variety of organisms. Initiation and maintenance of grooming bouts in order to remove foreign, interfering debris enables organisms to fully utilize sensory and motor systems necessary for survival and propagation of the species. In the fruit fly, *Drosophila melanogaster*, grooming has long been recognized as an innate behavior subject to variability between individuals. These observations indicate that grooming behaviors may be able to be characterized as quantitative traits, or quantifiable traits with continuous variation in a population. This project examines the hypothesis that natural variation in grooming behavior is driven by genetic variation in fly populations, and, by extension, that specific genetic variants of small effect contribute additively to the expression of this complex behavior. We utilized a subset of the *Drosophila* Genetic Reference Panel (DGRP), a population of ~200 inbred fly lines, to study genetic influences in grooming. This resource allows for relatively straightforward whole genome association mapping of loci associated with the quantitative traits being studied. This pilot project sought to examine grooming in a select subset of the DGRP in order to establish grooming as a quantitative trait and examine preliminary differences in populations in various grooming metrics, including total grooming time, grooming bout length, and the number of grooming bouts

in a specified time. We recorded behavior from more than 750 animals from 35 DGRP lines and scored them for grooming behaviors using freely available video annotation software. There is a continual gradation of all grooming metrics analyzed across the different DGRP lines, suggesting that these traits have genetic components influencing their differential expression between lines. Whole genome association analysis, although preliminary, points to several genomic regions of slight effect on grooming, including several known nervous system genes. Among the most promising genes influencing grooming are the locomotor rhythm regulator *dyschronic* (*dysc*) and the metabotropic glutamate receptor gene *mangetout* (*mtt*). Continuations of this study will focus on extending phenotypic classification of grooming to all ~200 DGRP lines using automated behavior scoring software and detailed genetic analysis of these preliminary association loci.

Disclosures: C.L. Hannum: None. **D.R. Andrew:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: NIH Grant RO1 AA018037

Title: Putative non-nuclear splice isoform of *Drosophila* NfkB Dif plays a role in ethanol response

Authors: *T. WIJESEKERA, N. ATKINSON
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Abstract: Chronic alcohol consumption has been shown to affect conserved gene networks in the human brain; one such network being the innate immune system. The Toll signaling pathway of the innate immune system is known to have a role in ethanol response, and has been successfully modeled in *Drosophila melanogaster*. The innate immune system of flies consists of the Toll and IMD (Immune Deficiency) pathways, which have evidence of cross-talk. The two pathways culminate at the NfkB proteins Dorsal, Dif (Dorsal like immunity factor) at Toll signaling, and Relish at IMD signaling. These pathways were shown to be important in ethanol response in flies as manipulating their expression changes sensitivity to ethanol. The above study identified an ethanol sensitivity phenotype for Dif. *dorsal* and *Dif* are expressed in alternative splice isoforms. The two isoforms of *dorsal* have different expression patterns and while Dorsal protein, containing a nuclear localization signal, is transported to the nucleus, Dorsal B is non-nuclear. Based on similarity between Dorsal and Dif, it is hypothesized that Dif A is nuclear and Dif B is non- nuclear. This study explores if the effect of Dif mutants on ethanol responses is splice-variant specific. The function of the two isoforms was tested using fly lines that are Dif

null, while engineered to express a specific (A or B) isoform. mRNA expression analysis of the fly lines shows absence of expression of the respective isoform while expressing the alternative isoform. Flies deficient in Dif B show a reduction in sensitivity to ethanol induced sedation as indicated by a significant decrease in KD50 (time for 50% sedation) of flies. Absence of the Dif A isoform does not change sensitivity to ethanol. The phenotype was seen to be recessive, as the sensitivity phenotype requires a homozygous Dif B mutant. It was also seen to be independent of the gender of the fly. Additionally, the sensitivity shown by Dif B mutant flies was also observed when measured as a rate of recovery from ethanol induced sedation, as an increase in R50 (time to 50% recovery) of flies. Comparison of the Dif null mutant and the Dif B mutant in ethanol induced sedation indicate that the sensitivity phenotype of Dif is caused by the putative non-nuclear B isoform. We document the expression of Dif B in the mushroom bodies of the adult brain, further strengthening the significance of the isoform in ethanol response.

Disclosures: T. Wijesekera: None. **N. Atkinson:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: NSF Grant IOS

Title: Flying *Drosophila* maintain arbitrary but stable headings relative to the angle of polarized light

Authors: *T. L. WARREN[1], P. T. WEIR[2], M. H. DICKINSON[3]
[1]Inst. of Neurosci., Univ. of Oregon, Eugene, OR; [3]Biol. and Bioengineering, [2]Caltech, Pasadena, CA

Abstract: Many animals disperse over long spatial scales in search of food, refuge, or mates. Efficient long distance travel requires the use of external orientation cues to maintain a straight course. Among possible cues, celestial features such as the sun or stars provide the most reliable landmarks for orientation. To move in a straight line, animals could either direct their motion towards or away from an object or, alternatively, maintain a heading that keeps the target at some fixed azimuthal orientation - a strategy termed proportional navigation. In this study we investigated how the fruit fly (*Drosophila melanogaster*) selects and maintains a heading in flight relative to the axis of linearly polarized light, a visual cue produced by the atmospheric scattering of sunlight and detected by many insects. To track flies' headings over extended periods, we used a flight simulator in which we coupled the angular velocity of a dorsal field of polarized light to the stroke amplitude difference of the animal’s two wings. Thus, flies could

adjust their wing strokes to choose a heading relative to the axis of polarized light as in free flight. In the simulator, flies stabilized rotation of linearly polarized light but not circularly polarized light, a control stimulus in which directional polarization cues are eliminated but unintended intensity cues are preserved. We observed that flies maintained a stable heading relative to the polarization axis for flights lasting ten minutes or longer. We found that flies selected headings in arbitrary directions relative to the polarization axis, rather than along or perpendicular to the polarization axis as has been previously reported. When flies flew in two consecutive flights, separated by a 5 minute gap without flying, we observed that flies' heading in the second flight was biased towards the prior flight heading. This suggests that flies retain a memory of the initial flight heading as well as an impetus to maintain it. Furthermore, we observed that flies' capacity to maintain a stable heading gradually increased over several minutes in an initial flight bout. These findings are consistent with a model in which individuals initially fly haphazardly in different directions, then subsequently gradually settle on a random heading, which they then lock into faithfully via a self-reinforcing monitoring process. Taken together, our data indicate that flies choose variable flights headings but then maintain them stably within a flight bout. Selecting random directions of dispersal may be a general strategy, shared across insects and other animals, for finding shelter and resources in unknown terrain.

Disclosures: T.L. Warren: None. **P.T. Weir:** None. **M.H. Dickinson:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Program#/Poster#: 156.10/LL13

Topic: F.01. Neuroethology

Support: NSF IOS-1455869

Title: Internal state modulates the perception of visual and olfactory stimuli by *Drosophila melanogaster*

Authors: R. MERNOFF[1], G. TURNER[2], P. LU[1], A. WANG[1], M. FRYE[1], *S. M. WASSERMAN[2]
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Abstract: Organisms rapidly evaluate the quality of their surroundings to make decisions to organize behavior. However, a singular input does not always elicit the same output. An animal's external environment and internal physiological state can influence the processes by which an animal assigns valence (positive or negative) to and prioritizes external stimuli within a noisy sensory environment. We utilize behavioral and physiological assays wherein quantitative feedback allows the animal to actively control its sensory experience in real time. In combination

with genetic, optogenetic, and physiological assays, we investigate the circuitry that permits an animal to produce adaptive behavioral responses in the face of changing internal and external conditions. Our data indicate that while well-fed and hydrated flies will assign a neutral valence to a water plume, acute dehydration and starvation result in an attractive response. Our findings also show that this modulation of internal state makes visual stimuli more salient in both behavioral and physiological assays. Preliminary data suggests that a subset of aminergic neurons in the brain could be responsible for modulating the saliency of water and visual stimuli in an altered internal state.

Disclosures: R. Mernoff: None. **G. Turner:** None. **P. Lu:** None. **A. Wang:** None. **M. Frye:** None. **S.M. Wasserman:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Topic: F.01. Neuroethology

Support: NIH F31 NS086283

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NSF IOS 1353075

Title: Sexual modulation of a shared sensory circuit by a conserved transcription factor

Authors: *D. S. PORTMAN[1], K. A. FAGAN[2], J. LUO[2], R. LAGOY[3], D. ALBRECHT[3], F. SCHROEDER[4]
[1]Ctr. for Neural Develop. and Dis., [2]Univ. of Rochester, Rochester, NY; [3]Worcester Polytechnic Inst., Worcester, MA; [4]Boyce Thompson Inst., Ithaca, NY

Abstract: The modulation of neural circuits and behavior by biological sex is a fundamental, yet poorly understood, aspect of neural plasticity. The compact nervous system of the nematode *C. elegans* provides an ideal model in which to explore these mechanisms. The two sexes of this species, the hermaphrodite (a self-fertile female) and the male, exhibit distinct responses to a variety of sensory cues, particularly the ascaroside-family sex pheromone ascr#3. While hermaphrodites are weakly repelled by ascr#3, males are strongly attracted to it. We find that this sexual dimorphism in behavior is generated not by hormonal signals, but rather by the genetic sex of circuits common to both sexes. *C. elegans* sexual differentiation depends on sex chromosome state (XX or X0) and is implemented by *tra-1*, the master transcriptional regulator that is both necessary and sufficient for female development and physiology. We find that ectopic activation of *tra-1* in the male nervous system blocks ascr#3 attraction; moreover,

inhibition of *tra-1* in the hermaphrodite nervous system is sufficient to generate ascr#3 attraction. To identify the cellular focus of genetic sex, we progressively restricted sex-reversal to subsets of the nervous system, eventually identifying a single sensory neuron pair, ADF, as the determinant of the response to ascr#3. In an otherwise wild-type animal, sex-reversal of ADF alone is sufficient to reprogram ascr#3-mediated behavior to that typical of the opposite sex. ADF controls this through sexually differentiated physiology: in males, ADF is strongly activated by ascarosides, but in hermaphrodites, ADF is insensitive to this stimulus. This sexual dimorphism is likely adaptive, as ADF-feminized males are substantially impaired in their ability to locate hermaphrodite mates. Furthermore, the *doublesex*-family transcription factor *mab-3*, previously shown to be male-specifically expressed in ADF, acts in this neuron to promote its sexually differentiated function. Together, our results illustrate a mechanism whereby sex-dependent tuning of sensory function generates adaptive plasticity in a shared neural circuit.

Disclosures: D.S. Portman: None. **K.A. Fagan:** None. **J. Luo:** None. **R. Lagoy:** None. **D. Albrecht:** None. **F. Schroeder:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Developmental Research and Creativity Grant, SFSU

NIH Grant 5R25GM050078

Title: Sensitization of the defensive strike response in Manduca sexta larvae is blocked during feeding

Authors: *M. FUSE[1], C. VALTIERRA[2], G. DOWNING[1], D. TABUENA[1], C. MOFFATT[1]
[1]Biol., San Francisco State Univ., San Francisco, CA; [2]Biol., City Col. of San Francisco, San Francisco, CA

Abstract: The defensive strike response in the hornworm, *Manduca sexta*, has been used to study pain-like responses under different conditions. For instance, following a noxious stimulus such as extreme cold or a pinch, the defensive strike response becomes sensitized. That is, sensitized animals become responsive to normally innocuous stimuli, indicative of a state of hyperalgesia. The goal of this research was to determine whether this behavior could be modified by other significant stimuli, such as might be provided by food to food-deprived larvae. After determining a baseline threshold to induce a defensive strike using the modified up-down

method with calibrated von Frey filaments, larvae were divided into fed and food-deprived ("starved") groups. These groups were then sensitized and tested with or without food. The threshold force required to elicit a defensive strike was determined before and after induction of sensitization, using a pinch as the noxious stimulus. All larvae showed a consistent high baseline threshold to elicit a defensive strike at the start of the experiment and after 24 hr, whether they were fed or not. However, after a pinch all groups showed a reduced threshold, indicative of sensitization, except for the starved group that was feeding. To determine whether this group had not been sensitized or whether their responsiveness to touch was merely attenuated by the presence of food, the food was removed and the larvae were tested again. Under this condition, the threshold was reduced, indicating that without food, sensitization was noted. These data suggest that the presence of food may represent an example of gate control theory in *M. sexta*. The role that octopamine, a monoamine implicated in feeding behaviors in insects, plays in this response will be addressed.

Disclosures: M. Fuse: None. **C. Valtierra:** None. **G. Downing:** None. **D. Tabuena:** None. **C. Moffatt:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Topic: D.05. Olfaction and Taste

Support: USAFOSR FA9550-17-1-0117

NIH 1 RO3 DC013997-01

Title: Evolutionary exaptation of an ancient motor-to-sensory circuit correlates with changes in insect flight biomechanics

Authors: *P. D. CHAPMAN, S. BRADLEY, K. RIGGS, E. HAUGHT, M. HAFFAR, K. C. DALY, A. M. DACKS
Biol., West Virginia Univ., Morgantown, WV

Abstract: Changes in behavioral ecology drive the evolution of neural circuits, yet the consequences of selective pressures associated with changes in behavioral ecology are rarely examined at a level of identified neurons. This study examines one form of circuit level evolution, exaptation, where individual neural circuits take on novel roles by providing information to new brain areas. We characterize the innervation of an identified histaminergic motor-to-sensory (flight/olfactory) circuit within Lepidoptera (the moths and butterflies) to determine that projections to the primary olfactory neuropil (the antennal lobe) across species is

heterogeneous. We hypothesized that changes in flight biomechanics underlie this heterogeneity. Therefore, we examined species across major groups within Lepidoptera with differing flight biomechanics, and provide evidence that butterflies (stochastic flight patterns relative to moths) do not use this flight-olfactory circuit. Additionally, caddisflies and microlepidopteran moths (both evolutionarily basal to butterflies) possess this circuitry suggesting that olfactory innervation was lost in butterflies. Finally, within more basal arthropods, we provide evidence that histaminergic motor-to-sensory connections are a common feature of arthropod CNS architecture. These neurons therefore represent an example of exaptation of an evolutionarily conserved motor-sensory circuit to perform an additional olfactory function in moths.

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Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.14/LL17

Topic: F.01. Neuroethology

Title: Escape behavior of the Grammostola rosea tarantula and Phiddipus regius spider in response to heat stimuli

Authors: *M. D. THOMAS, C. L. CLELAND
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Insects often respond to aversive stimuli such as wind, looming objects, and heat by escaping in a direction opposite the stimuli. Spiders and tarantulas, because they have eight legs, have potentially a greater repertoire escape responses. However, there are few published studies on their escape responses, especially regarding the effects of stimulus location or direction. The specific aim of this project was to determine the relationship between the stimulus location and direction of response in *Phiddipus regius (*Regal jumping spider) and juvenile *Grammostola rosea (*Chilean Rose tarantula) for heat stimuli delivered to the tarsi of the spider's eight legs. Chilean rose tarantulas were chosen because they are docile and readily obtained while jumping spiders are attractive because they have complex, "intelligent", predatory strategies. To evoke an escape response, the tarsi of each of its 8 legs was stimulated in random order at 5 minute intervals with an infrared laser (980 nm). The resulting escape response was captured with high-speed video (300 fps). Following the experiment, movement was tracked (Proanalyst), allowing quantification of the animals' location and orientation over time. Jumping spiders (n=5) and tarantulas (n=9) displayed both similar and differing responses. For both, the first response was to withdraw the stimulated leg and translate its body directly away from the stimulus, often without turning. Subsequently, both would turn away from the side stimulated and walk varying

distances. In contrast to tarantulas, jumping spiders often (~30%) continued to turn until orientating toward the location at which its tarsus was stimulated, and then stopping. These preliminary results demonstrate that tarantulas and spiders, like insects, have a well-organized response to aversive stimuli. The response of the jumping spider, in which it often stopped facing the location of the stimulus, may reflect its reliance on high quality vision and aggressive responses to potential predators.

Disclosures: M.D. Thomas: None. **C.L. Cleland:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Program#/Poster#: 156.15/LL18

Topic: F.01. Neuroethology

Title: Untangling a web of behaviors: Investigating the neuronal basis of web-building behavior by orb-weaving spiders

Authors: *A. GORDUS[1], J. MILLER[2]
[2]Biol., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The ability to encode a cognitive map of the environment in neuronal networks is a fascinating feature observed in vertebrate brains, and more recently in invertebrates. Orb-weaving spiders provide an excellent opportunity for understanding how spatial cognition can be utilized in a complex behavioral pattern that is encoded in a simple brain. Not only does the animal need to search its environment for an appropriate location, but it must also alter its surroundings to create a structure. This behavior requires external and internal cues to trigger and coordinate behaviors over multiple timescales to effectively construct something that may take hours to build. Construction also requires error correction to accommodate imperfections, and spatial cognition to effectively know not only where the animal is in space, but also where its structure is as well. An exceptional example of this behavior is spider orb-web weaving. It is remarkable for two reasons: 1) It is a structure that is not simply the accumulation of material around an individual or object (e.g. nest building), nor the displacement of mass (e.g. burrowing). It is the creation of a geometrically ordered abstraction in space, using material (silk) produced by the animal itself. 2) This behavior, which spans hours and involves the coordination of many sub-behaviors, is encoded in a brain no larger than a fly's. Our group seeks to understand this behavior at a fine spatiotemporal scale, and to uncover how this behavior is encoded at both the cellular and genetic level.

Disclosures: A. Gordus: None. **J. Miller:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Program#/Poster#: 156.16/LL19

Topic: F.01. Neuroethology

Support: CSU Provost Summer Undergraduate Research

Title: Analysis of the choices of African Clawed Toads (Xenopus laevis) when presented with paired visual and lateral line stimuli

Authors: *R. DEAN, B. YUGO, A. M. MAROTTA, M. ROLINCE, M. MILOSAVLJEVIC, K. GOTH, N. PAPENHAGEN, G. TAYLOR, A. DESHMUKH, C. IYASERE, A. SCHAFFER
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Abstract: African Clawed toads (*Xenopus laevis*) are aquatic toads that use both vision and their lateral line system to detect prey or predators at a distance. Appropriate stimuli elicit a rapid stereotyped turn and often approach and strike. Much research with adult toads has tested accuracy of turning to single stimuli. Our previous work has compared turns towards separate lateral line and visual stimuli. Here we compare responses to stimuli of both modalities presented as one stimulus or as a pair of stimuli. In particular, we analyze the choices the animals make when presented with two stimuli at the same time. Our study focused on how four variables—distance, angle, time of arrival, and visual prominence—influence toads' responses when simultaneously given two stimuli—Plexiglas rods briefly dipped into the water. One or two stimuli were presented each trial. The reactions of the toad were videotaped and then captured in sets of frames of stimuli and response. For each trial, stimulus angles and distances relative to the toad were measured before and after the toad's response. The toad's choice of stimulus was analyzed both as the stimulus location closer to the toad after its response and as the stimulus location closer to the toad's heading after the response. These criteria agreed for the majority of responses. Further, using these criteria, turning accuracy to the chosen stimulus was similar to that for a single stimulus. With respect to choice, results indicate: 1) toads preferably turned toward the closer stimulus, 2) toads preferably turned towards the more rostral stimulus, and 3) toads responded slightly more often to rods with a black mark than to clear rods, but this effect was weak. Relative distance was generally the strongest determinant of choice. Propagation of surface waves is complex with velocity and attenuation both depending on frequency. Thus, both relative times of arrival and wave amplitudes naturally reflect stimulus distance; on its own, time of arrival was not a significant factor in choice. However, more data are required. Response frequency in some animals slightly decreased when two wave stimuli arrived simultaneously.

Disclosures: **R. Dean:** None. **B. Yugo:** None. **A.M. Marotta:** None. **M. Rolince:** None. **M. Milosavljevic:** None. **K. Goth:** None. **N. Papenhagen:** None. **G. Taylor:** None. **A. Deshmukh:** None. **C. Iyasere:** None. **A. Schaffer:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.17/LL20

Topic: F.01. Neuroethology

Support: Department of Biological Sciences, Wright State University

Title: Respiratory motor frequency in bullfrog brainstems remains thermally stable across high, but not low, temperatures

Authors: *M. VALLEJO[1], J. SANTIN[2], L. K. HARTZLER[1]
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Abstract: Mechanisms that maintain robustness against environmental insults in vertebrate brains remain poorly understood. Many neurophysiological processes are temperature sensitive, but robustness of neural circuits are essential for maintaining normal neural function and behavior. Animals that cannot maintain body temperature in the face of ambient temperature changes, such as frogs, may undergo temperature changes of ~20°C in one day (Stevenson, 1985). Drastic temperature disturbances are predicted to destabilize neural circuits, but the circuit that controls breathing can maintain stable function over a 10°C range (15-25°C). To begin to identify mechanisms underlying stability of the respiratory network in frogs, we used brainstem-spinal cord preparations that produce spontaneously active, rhythmic motor output similar to breathing *in vivo* from adult bullfrogs, *Lithobates catesbeianus*. Preparations were superfused with artificial cerebrospinal fluid (aCSF) equilibrated at 90% O_2, 1.3% CO_2, and balance N_2. Whole nerve recordings from the trigeminal (V) and vagus (X) nerves were used for measuring respiratory-related activity. After obtaining stable baseline bursting we applied temperature ramps from 20ºC to 15ºC and then to 25ºC; each step lasted 15 minutes and bursting frequency was analyzed for the last 5 minutes of each step and then normalized to percent of baseline (20ºC). Contrary to previous findings (Morales and Hedrick, 2002), we demonstrate that the frequency of respiratory-related nerve activity is stable across high temperatures, but not lower temperatures (One-way ANOVA p=0.0004; percent of baseline significantly lower at 15ºC compared to 20ºC and compared to 25ºC, but no difference between 20ºC and 25ºC; Tukey's Multiple Comparison Test). Interestingly, this is consistent with the temperature at the transition from lung to skin gas exchange for CO_2 elimination. The locus coeruleus (LC) is a nucleus of the respiratory network and the main supplier of norepinephrine in the brain. LC neurons from bullfrogs are paradoxically activated by decreases in temperature (Santin et al., 2013) suggesting

that firing frequencies inversely proportional to temperature may play a role in stabilizing the respiratory network across higher temperatures. Preliminary data indicate that transection of the rostral brainstem and midbrain, containing the LC, disrupts stable bursting from 20-25°C. This implies that the LC may stabilize the respiratory network across warm temperature to meet metabolic demands and acid-base regulation requirements.

Disclosures: M. Vallejo: None. **J. Santin:** None. **L.K. Hartzler:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.18/LL21

Topic: F.01. Neuroethology

Title: Unveiling the mechanisms that underlie reduced responsiveness in larval zebrafish to uncontrollable stimuli

Authors: *K. J. HERRERA, F. ENGERT
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Abstract: Animals perform behaviors to achieve specific goals. These include actions as diverse as hunting or foraging to acquire food or escape-type behaviors to remove a noxious or threatening stimulus. However, behaving costs energy, necessitating the ability to decrease the frequency of actions that are identified as ineffective for achieving their goal. Here, we seek to determine potential neural circuits that regulate this ability in the larval zebrafish. We examine the changes in behavioral responses of the larval zebrafish to a noxious stimulus - high sodium chloride -in two paradigms: one where the action of the animal results in removal of the stimulus and another where actions have no effect. Our experiments find that when this noxious stimulus is inescapable, the larvae will reduce its likelihood of a response. Using light sheet microscopy to perform volumetric imaging during this task we then seek to identify the neural correlates of the alteration of the sensorimotor transformation. Our results suggest that a competitive balance between noradrenergic neural signaling that downregulates behavior and serotonergic activity that reinforces behaviors may be responsible.

Disclosures: K.J. Herrera: None. **F. Engert:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

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Topic: F.01. Neuroethology

Support: NSERC Discovery Grant 261405

Ontario Graduate Scholarship

U Windsor Entrance Scholarship

Title: An analysis of auditory-environment-dependent neuroplasticity in Danio rerio

Authors: M. K. MACKSOUD, *D. M. HIGGS
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Abstract: Acoustic experience-mediated neuroplasticity has been well defined in mammals and birds but, in many respects, has been less well studied in fish. Because of the enhanced ability of teleosts for central neurogenesis throughout adulthood, they represent a powerful system for investigation of environmental drivers on neuroplasticity. While overall environmental enrichment has been shown to increase central proliferation in teleosts, effects of exposure to defined sensory stimuli are less well examined and acoustic experience-mediated central neuroplasticity in teleosts has been scarcely investigated. In the current study, zebrafish (*Danio rerio*) were used to examine the effects of long-term sound exposure on the neuroplasticity of the central auditory system. Zebrafish were exposed to a continuous tone of 100, 200, 800, or 1000 Hz at 140 dB (re 1μPa) for a short-term duration of one hour or a long-term duration of one, two, three, or four weeks. Neuroplasticity is being quantified by changes in proliferation markers (PCNA), activity markers (phospho-S6 ribosomal protein), and in expression of genes with known neural function. To date we have seen increases in rates of cellular proliferation with duration of tone exposure, suggesting a clear effect of auditory exposure on proliferation of neurons in ascending central auditory areas. Quantification of neural activity and gene expression are still being quantified but hold potential in elucidating which specific gene products are affected in the central nervous system by peripheral sensory exposure. The present study demonstrates the neuroplastic potential of the zebrafish central auditory system in response to long-term sound exposure and proposes potential mechanisms underlying acoustic experience-mediated neuroplasticity in the teleost brain.

Disclosures: M.K. Macksoud: None. **D.M. Higgs:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

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Max Planck Gesselschaft

Title: A novel mechanism for mechanosensory based rheotaxis in larval zebrafish

Authors: *P. A. OTEIZA[1,2], I. ODSTRCIL[3], G. LAUDER[4], R. PORTUGUES[5], F. ENGERT[2]
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Abstract: When flying or swimming, animals must adjust their own movement to compensate for displacements induced by the flow of the surrounding air or water. These flow-induced displacements can most easily be detected as visual whole field motion with respect to the animal's frame of reference. In spite of this, many aquatic animals consistently orient and swim against oncoming flows (a behavior known as rheotaxis) even in the absence of visual cues. How animals achieve this task, and its underlying sensory basis, is still unknown. Here we show that in the absence of visual information, larval zebrafish (*Danio rerio*) perform rheotaxis by using flow velocity gradients as navigational cues. We present behavioral data that support a novel algorithm based on such local velocity gradients that fish use to efficiently avoid getting dragged by flowing water. Specifically, we show that fish use their mechanosensory lateral line to first sense the curl (or vorticity) of the local velocity vector field to detect the presence of flow and, second, measure its temporal change following swim bouts to deduce flow direction. These results reveal an elegant navigational strategy based on the sensing of flow velocity gradients and provide a comprehensive behavioral algorithm, also applicable for robotic design, that generalizes to a wide range of animal behaviors in moving fluids.

Disclosures: **P.A. Oteiza:** None. **I. Odstrcil:** None. **G. Lauder:** None. **R. Portugues:** None. **F. Engert:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.21/LL24

Topic: F.01. Neuroethology

Title: Identified neuronal circuit that controls prepulse inhibition of startle

Authors: *K. M. TABOR[1], C. HARRIS[2], T. SMITH[1], K. L. BRIGGMAN[2], H. A. BURGESS[1]
[1]NICHD, [2]NINDS, NIH, Bethesda, MD

Abstract: The startle reflex protects against dangers like predator strikes; a single failed startle may be fatal. Though potentially life-saving, this response interrupts concurrent behaviors and cognition and rapidly activates large muscle regions. Therefore, costly extraneous startles are suppressed when unneeded. One form of startle modulation with biological and medical consequence is acoustic prepulse inhibition (PPI), in which a weak prepulse presented before a strong 'startle' pulse suppresses the reflex. Dysregulated PPI is linked to psychiatric disorders, including schizophrenia. Yet discovering the neural basis of PPI is hampered by the lack of a defined vertebrate neural circuit. To resolve this, we have identified the specific neurons that control PPI of larval zebrafish. Previous work has demonstrated that neurons expressing Gsx1 are necessary for PPI in both mice and zebrafish. Using a Gsx1:Gal4 line to drive GCaMP6s expression and large-scale calcium imaging, we detected Gsx1 neurons with increased activity during PPI behavior. PPI-active Gsx1 neurons are bilaterally clustered in rhombomere 4 of the hindbrain, immediately dorsal to the pair of 'motor command' Mauthner cells, which trigger the startle response. To determine if these neurons are required for PPI we ablated these small clusters using 2 targeting approaches. First, we established a Gal4∩Cre intersectional genetic strategy to selectively ablate different subdivisions of the Gsx1 population. For this we developed a Cre library of 40 lines that specify discrete brain regions, including specific rhombomeres. Second, we used laser-targeted ablation of labeled glutamatergic Gsx1 neurons. Together, these ablation strategies showed that the loss of glutamatergic Gsx1 neurons in rhombomere 4 abolished PPI, demonstrating that these neurons are needed for PPI. Next, to test if these neurons are sufficient for PPI, we selectively activated Gsx1 neurons expressing channelrhodopsin with rhombomere 4-focused light in optogenetic-acoustic PPI tests. Direct activation of the neurons inhibited the behavioral response to a following acoustic 'startle' pulse, confirming that these neurons implement PPI. Moreover, to reveal where these neurons contact the startle circuit, we established a triple genetic intersect approach exploiting the inefficient B3 recombinase system to label individual neurons in the clusters. 83% of reconstructed neurons

project to the ipsilateral ‘motor command’ cell, and 75% send projects to its contralateral counterpart. Here, we have identified with cellular resolution the zebrafish PPI circuit.

Disclosures: K.M. Tabor: None. **C. Harris:** None. **T. Smith:** None. **K.L. Briggman:** None. **H.A. Burgess:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Topic: F.01. Neuroethology

Support: NSF Grant IOS 1557895

Title: Differences in electromotor behaviors in blind electric cavefish and their surface relatives

Authors: *E. S. FORTUNE[1], N. ANDANAR[1], M. MADHAV[2], R. JAYAKUMAR[2], N. COWAN[2], M. BICHUETTE[3], D. SOARES[1]
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Abstract: Troglobitic animals often exhibit dramatic differences in behavior and in the size and structure of sensory organs when compared to their epigean relatives. These differences can include the loss of eyes and the emergence or elaboration of other sensory organs. Recently, a species of troglobitic *Eigenmannia* (a genus of Gymnotiform weakly electric fishes) was discovered in a cave in Brazil (San Vincente II) within the Terra Ronca State Park (13°30' - 13°50' S, 46°0' - 46°30’W). We compared electromotor behaviors and the morphology of electrosensory systems of these cavefish with their epigean relatives from a nearby river (Rio da Lapa). Electrosocial and swimming behaviors were recorded at these field sites using a 16-electrode grid with 0.5 meter spacing that was placed into the streams. Fish swam freely through the grid and could be visually observed in the crystal clear water of this watershed. The epigean *Eigenmannia* showed a diurnal pattern of locomotor and signalling behavior, hiding in rocks and root systems along the sides of the streams and rivers during daylight hours, but emerging overnight with active swimming over distances of at least several meters. During the day, epigean *Eigenmannia* maintained nearly constant electric field frequencies, whereas at night these animals modulated their electric field frequencies. These modulations are similar to previously described social signals in this genus. In contrast, we saw no evidence of diurnal modulation of behavior in the hypogean *Eigenmannia*. These fish, which are either eyeless or have vestigial eyes, made short-duration excursions into slower-moving open water from their rocky hiding places on the edges of the stream. Underwater videos showed that these fish can make precise movements relative to conspecifics in the absence of visual cues. The hypogean

fish produced similar categories of modulations of the electric fields as seen in the epigean fish. However, the electric field strength of the hypogean fish were dramatically increased relative to their epigean relatives. We made CT scans of 3 epigean and 3 hypogean *Eigenmannia*: the electric organs of the hypogean fish were hypertrophied relative to the epigean fish.

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Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.23/LL26

Topic: F.01. Neuroethology

Support: NSF IOS 1557846

Title: Matching neural coding strategies to behavior: Responses to communication signals in the hindbrain of Apteronotids

Authors: *G. MARSAT, K. M. ALLEN
Biol., West Virginia Univ., Morgantown, WV

Abstract: Reliable transmission of information from sender to receiver is crucial for all species, but the format of this exchange may be highly variable. Diverse species face diverse constraints on communication, such as environmental noise, predation risk, and social competition, but even closely related species may develop highly varied communication systems. As signal production varies, the sensory systems that receive the signal must also be adequately tuned to extract information from that signal. In a species of weakly electric fish, *Apteronotus albifrons* we examine the unique neurophysiological properties that support the efficient encoding of electrosensory information, particularly the signals that the animal would encounter in social exchanges. We compare our findings to known coding properties of the closely related species *Apteronotus leptorhynchus* to establish how these animals have tuned the electrosensory system for detection and discrimination of their distinctive communication signals. While there are many similarities between these two species, we find notable differences leading to relatively poor coding of chirp identity. As a result, small differences in chirps properties are poorly resolved by the nervous system. We performed several behavioral tests and signal analyses to understand how the differences between chirp coding between *A. albifrons* and *A. leptorhynchus* could be related to the way they use chirps behaviorally. Our results suggest that *A. albifrons* behavior does not rely on the exchange of frequent chirps with small variations in properties. Therefore, our study suggests that neural coding strategies are matched to the signals and behavioral tasks in a species-specific manner and varies even among closely related species.

Disclosures: **G. Marsat:** None. **K.M. Allen:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.24/LL27

Topic: F.01. Neuroethology

Title: Serotonergic-dependent SK channel neuromodulation adaptively optimizes neural coding and behavioral perception of natural sensory stimuli

Authors: *C. HUANG, M. G. METZEN, M. J. CHACRON
Dept. of Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Growing evidence suggests that sensory systems must continuously adapt in order to optimally encode natural stimuli with changing statistics (e.g., their probability of occurrence) within the natural environment. However, the nature of the underlying mechanisms remains poorly understood to this day. Here we investigated adaptive optimized coding of natural electrosensory stimuli experienced by the weakly-electric fish, *Apteronotus leptorhynchus*. Previous results have demonstrated that sensory pyramidal neurons within the electrosensory lateral line lobe (ELL) optimally encode natural stimuli whose power spectrum decays with power-law exponent α=-0.8 by implementing temporal whitening. Specifically, neural tuning, which is determined by small conductance calcium-activated potassium type 1 (SK1) channels is set such as to oppose the decaying stimulus spectrum.
Here we investigated whether optimized coding of natural electrosensory stimuli is adaptive to changes in stimulus statistics and whether changes in SK1 channel conductance mediated these changes. Specifically, we hypothesized that such changes are mediated by the centrifugal serotonergic fibers emanating from the raphe nuclei since previous studies have shown that activation of such fibers downregulates SK1 channels. We tested adaptive optimized coding by presenting animals with stimuli whose power spectrum decays with power-law exponents α=-2 or α=0. Using a combination of in-vivo electrophysiology, pharmacology, lesion paradigms, and behavioral paradigms, we found that pyramidal neurons in the ELL shifted their neural tuning curves in combination with their baseline activity to give rise to adaptive temporal whitening of the newly presented stimulus statistics, thereby leading to matched behavioral perception. In addition, our results demonstrate that this process critically depends on feedback from the telencephalon as lesioning the telencephalon resulted in a failure to adapt in both neural tuning and behavioral perception. Finally, our pharmacology studies revealed that serotonergic modulation on the dendritic SK1 channels on pyramidal neurons was also essential to this adaptation process. Our results thus reveal a novel functional role for the serotonergic system,

which is very well conserved across vertebrates. Hence, the parallels between the electrosensory and other sensory systems imply that our results are generally applicable.

Disclosures: C. Huang: None. **M.G. Metzen:** None. **M.J. Chacron:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: F.01. Neuroethology

Support: NSF ANT-1341602

Title: Motoric and respiratory behaviors of Antarctic fishes with and without hemoglobin in response to rise in ambient temperature

Authors: *I. I. ISMAILOV[1], J. B. SCHARPING[2], I. E. ANDREEVA[1], M. J. FRIEDLANDER[1]
[1]Virginia Tech. Carilion Res. Inst., Roanoke, VA; [2]Virginia Tech. Carilion Sch. of Med., Roanoke, VA

Abstract: Antarctic teleosts *C. aceratus* (lack hemoglobin, Hb-) and *N. coriiceps* (possess hemoglobin, Hb+) are extremely stenothermic and live at temperature (T) near 0°C. Hb- fishes are less tolerant to T elevation than Hb+ animals, but the nature of this difference is unknown. Our study investigated motoric (MB) and respiratory behaviors (RB) of Hb+ and Hb- fishes in response to acute warming, and their relation to nervous system (NS) malfunction. Both Hb+ and Hb- fishes exhibited two purposeful transient locomotor MB: 1) avoidance response - labriform swimming with initial T rise as little as 0.1°C; and 2) escape response - starting at ~+6°C with labriform swimming and peaking at ~+9°C in Hb- and ~+11°C in Hb+ with subcarangiform propulsion and C-start escape movements (only Hb+); accompanied throughout by spontaneous turning, reminiscent of C-turn startle responses (with pronounced directional bias only in Hb+ fish). Avoidance and escape were interleaved in both species at ~+2°C with a period of relative motionlessness (possibly, energy cost reduction). During this period, consistent with increase in metabolic demand and deepening hypoxia, both species gradually increased ventilation frequency (Vf) achieving a maximum at ~+8°C (*i.e.*, at the peak of escape response). Escape response was also accompanied by RB (gulping and aquatic surface respiration) in both species. Strategies to cope with further rise in T were different between the species. Hb- fish maintained maximal Vf, but entered into an energy cost reducing station holding mode, while exhibiting fanning - undulatory pectoral fin movements without translation (which we interpret as a RB, facilitating cutaneous and/or branchial gas exchange). Vf of Hb+ fish declined sharply after the peak at ~+8°C (before the peak of the escape response), suggesting that other mechanisms (*e.g.*, an increase in hematocrit) may have compensated for increased respiratory demand of these

animals at high T. Persistent C-turns represented most of MB in Hb+ fish at +12°C, with lateralization completely reversed (and attenuated above +14°C), suggesting onset of NS malfunction. Some specimens of Hb- fish also exhibited erratic C-turning, following rapid decline in Vf (onset T ~+12°C) just prior to the loss of equilibrium (LOE) at ~+14°C. In Hb+ fish, LOE occurred at ~+16°C, preceded by a surge of erratic C-start movements and surfacing in subcarangiform mode. We conclude that both Hb+ and Hb- Antarctic fishes possess a multitude of MB and RB to avoid and escape hazardous T, all similarly sensitive and well-orchestrated by the NS to prevent malfunction, that occurs only when an acute rise in T is unescapable.
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Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Topic: F.01. Neuroethology

Support: NSF Cooperative Agreement No. OIA-1458952

Title: Low-level, short-term manganese exposure has long-term effects on escape response and monoamine levels in juvenile Procambarus clarkii

Authors: A. B. PARSONS-WHITE, L. E. REASOR, G. A. BROWN, *B. L. ANTONSEN
Biol. Sci., Marshall Univ., Huntington, WV

Abstract: Long-term exposure to sub-clinical concentrations of Mn in drinking water have been linked to neuropsychological and behavioral defect, such as anxiety, depression, ADHD and hyperactivity in children and adolescents. Due to increased absorption and retention rates, excess Mn during infancy could have long-term effects on behavior and development, even when exposure time is brief. Here, we used an aquatic invertebrate model to examine the long-term effects of short-term, low-level manganese exposure during development. Male and female crayfish (*Procambarus clarkii*) were raised in the lab in artificial reconstituted fresh water with a 12/12 light cycle and regular feeding regime to post-embryonic stage 4. Following this, they were exposed to environmentally relevant concentrations of Mn ranging from 0.005mg/L to 1.0mg/L for either 2 days or 2 weeks while maintaining feeding and light schedules, then returned to reconstituted fresh water in isolation for 6 months. Control animals were treated the same, except they were put into clean reconstituted water for the exposure period. At 6 months, we analyzed their escape response to a perceived threat. Videos were analyzed using Ethovision XT behavior analysis software. Weight, length, and sex of each crayfish were recorded before

dissection, and immunohistochemistry was performed on nerve cords against serotonin (5-HT) and dopamine (DA). Nerve cord images were analyzed using Image J to determine distribution of 5-HT and DA label compared to control animals. Crayfish treated with elevated manganese levels for 2 days had significantly increased latency to escape and change in trajectory of escape such that they remained closer to the floor of the enclosure. Those treated for 2 days also had a dose dependent reduction in 5-HT and DA, weighed significantly more and were longer 6 months post treatment than control or 2 week treated crayfish. Crayfish treated for 2 weeks displayed high variability in escape response compared to the stereotypical response control animals, in several aspects of initial escape tail flip including velocity and trajectory. Crayfish treated for 2 weeks also had a dose dependent reduction of 5-HT and DA. They also weighed significantly less and were smaller than control or 2 day treated animals, with several crayfish showing signs of abdominal muscle tissue atrophy. Our data indicate that even short treatment with levels of manganese lower than EPA standard for drinking water can have long lasting impacts on behavior and neurophysiology of crayfish. This will impact the survival of these animals, suggesting long term impacts on aquatic ecosystems and potential issues for human health.

Disclosures: A.B. Parsons-White: None. **L.E. Reasor:** None. **G.A. Brown:** None. **B.L. Antonsen:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.27/LL30

Topic: F.01. Neuroethology

Title: Neuropharmacology of alcohol effects on crayfish neural circuitry

Authors: *J. HERBERHOLZ, M. E. SWIERZBINSKI, L. C. VENUTI, H. J. LEE, A. C. EXUM
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Abstract: Alcohol is a devastating drug that affects behavior after both acute and chronic exposure, leading to immediate and long-term challenges for human health and society. However, the interplay between alcohol and cellular neurochemistry is still poorly understood, in part because alcohol interacts with multiple neurotransmitter systems. We recently found that juvenile crayfish are behaviorally sensitive to alcohol, and during an early stage of intoxication, the animals produce uncontrolled sequences of rapid tail flexions (“tail-flips”). In the absence of alcohol, tail-flips are only observed in response to salient danger stimuli that mark a potential attack. We further documented that the behavioral effects of alcohol are manifested at the level of individual neurons that control certain tail-flips. Current experiments investigate the key

components of one tail-flip circuit, the medial giant [MG] interneurons. The MG neurons receive both visual and mechanosensory inputs in the brain, and once activated, their activity drives the animal backwards away from a frontal danger stimulus. MG tail-flips are used during escape from natural and simulated predator signals as well as during intraspecific aggressive interactions. Using intracellular electrophysiology combined with neuropharmacology, we measured the effects of alcohol on the excitability of the MG neurons. We found that alcohol lowers the threshold for MG firing, showing that the neural effects of alcohol generalize across different tail-flip circuits. Next, we investigated the interactions between alcohol and the γ-aminobutyric acid (GABA) system by measuring the role of muscimol (a $GABA_A$ receptor agonist) on alcohol-induced changes in MG excitability. Pretreatment with muscimol eliminated the stimulating effects of alcohol, and we are currently testing the effects of picrotoxin (a $GABA_A$ receptor antagonist). In parallel, we are injecting freely behaving crayfish with $GABA_A$ receptor agonists and antagonist before exposure to alcohol, and our preliminary results show that the animals' behavioral sensitivity to alcohol increases after pretreatment with a $GABA_A$ receptor antagonist. Taken together, we found that the neurobehavioral response of crayfish to acute alcohol exposure is mediated, at least in part, by cellular interactions between alcohol and the GABAergic system. This opens the door for identification of alcohol's conserved cellular-molecular mechanisms that can be measured in single neurons directly linked to whole animal behavior, which is difficult to accomplish in other current models of biomedical relevance.

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Poster

156. Neuroethology: Circuits and Behavioral Analyses

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Topic: F.01. Neuroethology

Support: Swiss National Foundation (Grant 31003A_127024)

Title: What are the roles of successful and unsuccessful trials during motor learning?

Authors: *A. T. ZAI, R. O. TACHIBANA, R. H. HAHNLOSER
Inst. of Neuroinformatics, ETH Zurich / Univ. of Zurich, Zuerich, Switzerland

Abstract: Reinforcement is one of the main strategies used to train animals ('good dog', 'bad dog'). Reinforcement learning strategies build upon the relationship between motor variability and reward to improve behavioral outcome (Williams, 1992; Wolpert et al., 2011). However, the biological mechanisms of reinforcement learning and their roles in skillful movement learning are still poorly understood.

How does the brain use information from successful and unsuccessful motor trials? Do neurobiological learning mechanisms rely more on successful motor trials (for example by memorizing them and learning to repeat them)? Or do they rely more on unsuccessful motor trials (for example by trying 'the opposite' or a new and contrasting approach)? We designed an experiment to distinguish these repeat vs. oppose models of reinforcement learning. Using electrical stimulation of a premotor brain area, we seek to behaviorally dissect the learning effects of successful and unsuccessful motor trials.
Birdsong learning provides a tractable model system to study the neural systems underlying reinforcement learning. In particular, we know that by electrically stimulating the lateral magnocellular nucleus of the anterior nidopallium (LMAN), it is possible to elicit small changes in animals' vocalizations (Kao et al. 2005). By stimulating LMAN during singing and aversively reinforcing (using white noise playback) non-stimulated songs, we teach birds to reproduce the stimulated songs even during non-stimulated trials (stimulated trials correspond to successful trials). If birds can learn to reproduce the songs elicited by stimulation, then birds can learn from successful trials (because non-successful trials contain no information about the song target). Similarly, by aversively reinforcing the stimulated trials, we teach birds to avoid the stimulated versions of their songs. In this second case, if birds learn to avoid the stimulated and unsuccessful versions, then birds can learn from unsuccessful trials.
Our data provide evidence that birds can efficiently use successful trials for learning because they can reproduce song versions evoked by electrical stimulation. On the other hand, motor changes from unsuccessful trials seem to be more variable and less goal-directed. Our results suggest that successful trials are more important for motor learning than unsuccessful trials.

Disclosures: A.T. Zai: None. **R.O. Tachibana:** None. **R.H. Hahnloser:** None.

Poster

156. Neuroethology: Circuits and Behavioral Analyses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 156.29/LL32

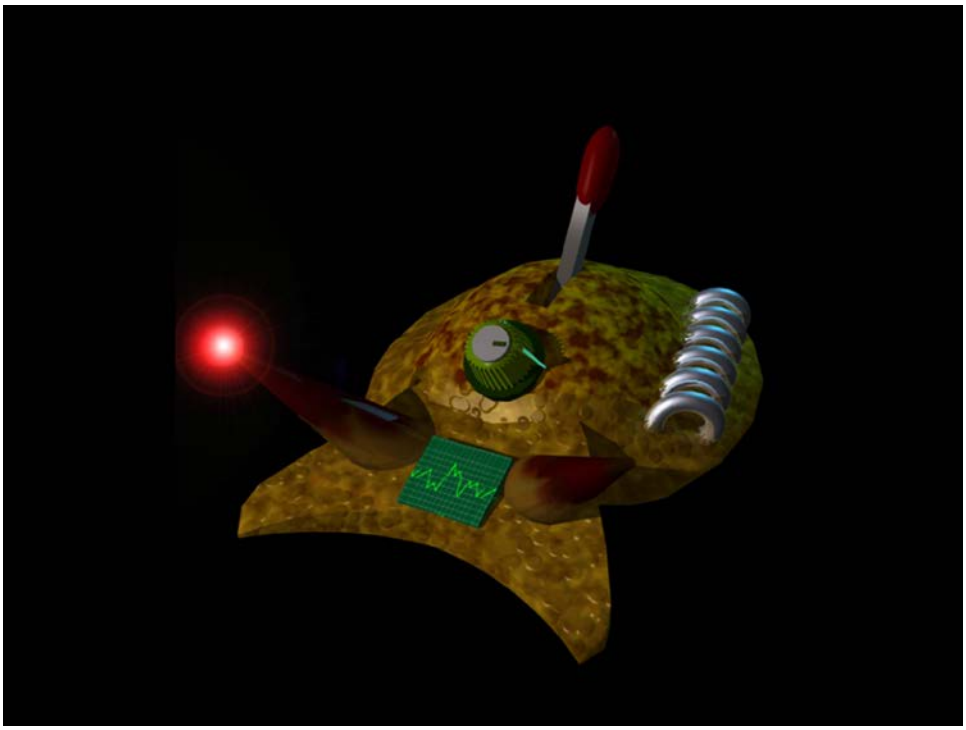
Topic: F.01. Neuroethology

Title: Modeling odor tracking computations in the peripheral nervous system of a predatory snail

Authors: M. VOLOSHIN[1], *M. U. GILLETTE[2], R. GILLETTE[2]
[1]Yow Time Enterprises, Brooklyn, NY; [2]Dept. of Cell & Developmental Biol., Univ. of Illinois, Urbana, IL

Abstract: Foraging animals tracking prey odor trails calculate efficient orienting and approach maneuvers. In the predatory sea-slug *Pleurobranchaea californica*, evidence suggests that the calculation for the target and magnitude of orienting movements is performed in the neuronal circuitry of the peripheral nervous system (PNS) at the chemotactile areas. Thus, sensory nerve

spike frequency is proportionate to the position of a chemotactile stimulus at the oral veil, indicating that the PNS can encode the turn amplitude before the signal reaches the central nervous system (Yafremava and Gillette, *J Neurophys* 105: 2885-2890, 2011). The computational mechanism remains open to conjecture and experimentally challenging, as the PNS has not yet been well explored electrophysiologically. However, many primary chemosensor cells are labeled for dopamine, and we found that topical application of the D2 blocker sulpiride numbs appetitive chemosensation, while D1 blockers have no effects. As D2 receptors are generally inhibitory, the mechanism of directional calculation may incorporate disinhibitory connections. With this information we propose a general model of the neural connectivity and computations in the PNS of the oral veil, emphasizing minimal supposition of unobserved components. The simulant's odor-tracking behavior qualitatively resembles that of the real animal. We incorporate the model into the interactive web-based animation Cyberslug™. The user observes a simulated *Pleurobranchaea* tracking a virtual odor plume in a mildly turbulent ocean current. We show the precise mechanisms of the model's operation and its predictions, which are subject to future experimental test in the animal.



Disclosures: **M. Voloshin:** None. **M.U. Gillette:** None. **R. Gillette:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.01/LL33

Topic: F.01. Neuroethology

Support: NIH Grant R01-MH096875

Title: Approaches to identify, impute, interpret and integrate functional genomic data using biobanked tissues from a population of free-ranging rhesus macaques

Authors: *M. J. MONTAGUE[1], N. SNYDER-MACKLER[2], L. J. BRENT[4], S. MADLON-KAY[1], J. E. HORVATH[5], J. SKENE[3], M. L. PLATT[1]
[1]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [2]Evolutionary Anthrop., [3]Neurobio., Duke Univ., Durham, NC; [4]Ctr. for Res. in Animal Behaviour, Univ. of Exeter, Exeter, United Kingdom; [5]Biol. & Biomed. Sci., North Carolina Central Univ., Durham, NC

Abstract: Evidence suggests that individual variation in social behavior arises from a combination of genetic predispositions and individual experience, yet the underlying biological mechanisms remain poorly understood. To address this gap, we have sought to understand the genetic contributions to social behavior in a large, free-ranging population of rhesus macaques (*Macaca mulatta*) with a known pedigree and detailed behavioral phenotypes. We hypothesized that genetic variants underlying molecular differences in neural circuits may be associated with behavioral variation in this socially complex species. Toward this end, over the past seven years, we have compiled genetic data and biological samples from approximately 1000 animals, while also amassing extensive behavioral and cognitive data through assays and focal observations. We have extracted DNA from whole blood and have conducted whole genome sequencing for over 250 individuals. Additional sampling includes skin, lung, fecal and digestive tract microbiota, as well as twenty peripheral tissues and organs sampled from hundreds of animals. Whole blood and flash frozen brain tissues are currently being used for gene expression (RNAseq) and epigenetic (ATAC-seq) analyses. The brain bank is unprecedented in the number, diversity of ages, and degree of background behavioral information. This multi-faceted approach will generate valuable insights on the influences of social environment, including not only social stressors, but also social mechanisms that may be protective against stress. Here, we illustrate how this integrative dataset can be used to identify the functions and pathways underlying the relationship between social environment and the transcriptional and epigenomic signatures in different brain regions.

Disclosures: M.J. Montague: None. **N. Snyder-Mackler:** None. **L.J. Brent:** None. **S. Madlon-Kay:** None. **J.E. Horvath:** None. **J. Skene:** None. **M.L. Platt:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.02/MM1

Topic: F.01. Neuroethology

Support: DFG EXC307

Title: External acoustic events induce rapid changes in vocal behavior of marmoset monkeys

Authors: *T. POMBERGER[1,2], J. LÖSCHNER[1,3], C. GLOGE[1], S. R. HAGE[4]
[1]Werner Reichardt Ctr. For Integrative Neuroscien, Tübingen, Germany; [2]Grad. Sch. of Neural & Behavioural Sci. - Intl. Max Planck Res. School, Univ. of Tübingen, Tübingen, Germany; [3]Animal Physiology, Inst. for Neurobiology, Univ. of Tübingen, Tübingen, Germany; [4]Werner Reichardt Ctr. for Integrative Neurosci., Tuebingen, Germany

Abstract: Vocal behavior is modulated by sensory feedback in both animals and humans. Vocal behavior in particular is modulated by acoustic feedback such as ambient noise or self-produced acoustic signals. Such acoustic events can cause distinct changes in acoustic parameters such as call frequency, amplitude and duration and the timing of vocal onset. These effects have been observed in several vertebrates, such as birds and mammals including humans. Recent studies indicate that some of these changes occur fast and independent of each other suggesting a complex audio-vocal integration system within the brain. In the present study, we investigate how external acoustic events such as ambient noise affect vocal behavior in the marmoset monkey (*Callithrix jacchus*). We find that external acoustic events exhibit rapid changes in distinct call parameters, while others seem to be unaffected. Our data give new insights into vocal motor control processes and audio-vocal integration mechanisms in the primate brain and will help to guide future neurophysiological experiments on this behavior.

Disclosures: T. Pomberger: None. **J. Löschner:** None. **C. Gloge:** None. **S.R. Hage:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.03/MM2

Topic: F.01. Neuroethology

Support: DFG EXC307

Title: Limiting parental feedback during vocal development influences vocal properties in marmoset monkeys

Authors: *Y. GÜLTEKIN[1], S. R. HAGE[2]
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Abstract: Vocalizations of human infants change dramatically across the first year by becoming increasingly mature and speech-like. Human vocal development is driven by learning from caretakers. Vocalizations of non-human primates are mainly innate and changes during development were thought to be purely due to maturation. Although non-human primate vocalizations are largely innate, recent studies revealed vocal developmental processes are influenced by parental feedback in marmoset monkeys. Marmosets produce infant-specific vocalizations that disappear after the first postnatal months. It was not yet clear whether parental feedback in mammals is, as in humans, an obligate requirement for proper vocal development, or whether it simply accelerates vocal development without a detrimental effect if absent. To address this question, we compared vocal behaviour of marmosets in the subadult stage. We used two sets of offspring from the same parents: one set was normally raised, while the other was separated from the parents after the third postnatal month. Using quantitative measures to compare distinct call parameters and vocal sequence structure of the litters, we showed that parental feedback is necessary for normal vocal development in marmosets. Both normally raised and limited parental feedback monkeys produced a variety of adult call types. However, while normally raised monkeys exclusively produced adult calls at the age of seven months, monkeys that had limited parental feedback still produced infant calls at the age of 13 months. In addition, limited parental feedback monkeys still exhibited the infant-specific babbling behaviour. In our recent study, we evaluated the acoustic properties of the vocalizations of both limited parental feedback and normally raised monkeys. Compared to their younger, normally raised siblings, we find that the older monkeys with limited parental feedback showed calls with more adult-like acoustic traits in most of their call utterances. However, our data show that one particular vocalization, the “phee” call, was still less mature in the older monkeys with limited parental feedback compared to the phees of their younger normally-raised siblings. Our data indicate that especially the vocal development of phee calls is affected by a lack of parental feedback supporting recent studies that hypothesize that phee calls in particular underlie significant changes during vocal development and that these changes are dependent on parental feedback. These findings suggest a significant role of social feedback on primate vocal development and further show that marmoset monkeys are a compelling model system for human vocal development

Disclosures: Y. Gültekin: None. **S.R. Hage:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.04/MM3

Topic: F.01. Neuroethology

Support: DFG HA5400/3-1

DFG EXC307

Title: Context-dependent modulation of vocal behavior in marmoset monkeys

Authors: *D. DOHMEN[1], S. R. HAGE[2]
[1]Neurobio. of Vocal Communication, W. Reichardt Ctr. For Integrative Neurosci. (, Tübingen, Germany; [2]Werner Reichardt Ctr. for Integrative Neurosci., Tuebingen, Germany

Abstract: A central aspect of human interaction is cooperative communication. Hereby, we follow certain implicit rules to optimize our communication. We take turns, for example as we communicate verbally or non-verbally with each other. While one person speaks, the other one remains silent until there's a gap of silence to reply and vice versa. Similarly to human verbal communication, the common marmoset monkey also adheres to a certain set of rules during vocal communication. As humans, they generally avoid to vocalize during the vocalization of a conspecific. Another example of implicit rules can be found in their long-distance communication in between individuals. As one monkey utters a so-called phee call, another individual will likely reply after a delay of 6-9 seconds [Miller et al. (2009) J Comp Physiol A]. This call, in turn, is then again answered with another phee call. Furthermore, it has been shown that the communicative content of these calls extends beyond just the information about the simple presence of another monkey. Information such as sex, age and identity of the signaler is embedded in the acoustic features of a vocalization [Miller & Thomas (2012) J Comp Physiol A]. In addition, it has been previously demonstrated that these calls are not just simple responses with fixed latency patterns, but rather underlie dynamic mechanisms that adjust in accordance to the communicative content of a distinct vocal exchange [Takahashi et al. (2013) Curr Biol, Choi et al. (2015) J Neurophysiol]. These findings indicate a complex neuronal network underlying this type of vocal behavior. In the current study, we investigate further characteristics of the turn-taking behavior in marmoset monkeys. We neuroethologically manipulated the communicative context of the antiphonal calling behavior and show that, additionally to previous findings, the vocal turn-taking behavior of these animals is context dependent. Our results further illustrate the dynamic nature of this audio-vocal behavior making it a good model system to investigate audio-vocal interactions in a highly vocal animal, the common marmoset.

Disclosures: D. Dohmen: None. **S.R. Hage:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.05/MM4

Topic: F.01. Neuroethology

Title: Sound source localization system reveals ultrasonic semantic communication in groups of freely interacting mice

Authors: D. T. SANGIAMO[1,2], M. R. WARREN[1], *J. P. NEUNUEBEL[1]
[1]Psychological and Brain Sci., Univ. of Delaware, Newark, DE; [2]Univ. of Illinois, Champaign, IL

Abstract: In the animal kingdom, innate social behaviors play a crucial role in survival and reproduction. For example, agonistic behaviors between males shape the formation of dominance hierarchies, allowing the prevailing male to access food, territory, and females (Dewsbury, 1982). In mice, agonistic behaviors are accompanied by ultrasonic vocalizations (USVs) (Gourbal et al., 2004) although some reports suggest that USVs are only produced during reproductive behaviors (Whitney et al., 1973). Conflicting evidence and limitations in the ability to determine which mice are vocalizing during a social interaction make the relationship between agonistic behavior and USVs unclear. Using a system adapted from Neunuebel et al. (2015) to assign vocal signals to individual animals and an automatic behavioral classifier program (Kabra et al., 2013), we investigated the relationship between USVs and agonistic behaviors. Subjects (11 groups of 2 males and 2 females; 12-21 weeks old B6.CAST-Cdh23Ahl+/Kjn) were allowed to freely interact for 5 hours. To determine when a male was chasing a male, fighting, fleeing, being chased, being fled from, circling another male, chasing a female, or walking, automatic behavioral classifiers were created. We discovered that mice emit vocal signals at significantly different rates during each behavior (1-way ANOVA, $F_{7,32344} = 1032.5$, $p < 10^{-8}$). Vocal signals were then grouped into separate types based on their general shape using a novel, automated clustering algorithm. Disparate vocal signals were emitted at different proportions depending on their type (2-way ANOVA, $F_{10,53559} = 451.0$, $p < 10^{-8}$). A significant interaction between type of vocal signal and behavior was observed (2-way ANOVA, $F_{70,53559} = 67.6$, $p < 10^{-8}$), revealing that vocal expression varies depending on the behavior. Using a bootstrap analysis, we showed that specific types of vocal signals were emitted at a proportion that was above chance by mice acting aggressively towards other mice, whereas other types of vocal signals were emitted at a proportion above chance by mice avoiding other animals. Vocal signal types that were emitted at a proportion above chance in one context were often emitted at a proportion that was below chance in other contexts. Lastly, we showed that vocal expression impacts the behavior of the mouse receiving these auditory signals. Both males and females slowed down when the mouse chasing them emitted a type of vocal signal that occurred above chance within a chase (Student's

t-test; M: t_{411}=7.3, $p < 10^{-8}$; F: t_{1899}= 11.8, $p < 10^{-8}$). In conclusion, our results reveal mice employ a rudimentary form of ultrasonic semantic communication that modulates behavior.

Disclosures: D.T. Sangiamo: None. **M.R. Warren:** None. **J.P. Neunuebel:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.06/MM5

Topic: F.01. Neuroethology

Title: Using sound source localization to investigate the impact of the reproductive cycle on mouse vocal expression

Authors: L. A. MECKLER, M. R. WARREN, M. S. SPURRIER, *E. ROTH, J. P. NEUNUEBEL
Psych and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Mice produce ultrasonic vocalizations (USVs) in a variety of social contexts, most notably courtship displays (Sales, 1972). Courtship behaviors are strongly influenced by the reproductive cycle of females (Haga-Yamanaka et al., 2014); however, the impact that the female's reproductive stage has on vocal communication is unclear. Although some studies have found no differences in vocal communication across the different stages of the reproductive cycle (Whitney & Nyby, 1979), others have revealed that the acoustic features of male vocalizations do change (Hanson & Hurley, 2012). Recent evidence indicates that female mice are vocally active during mixed-sex interactions (Neunuebel et al., 2015), adding an additional variable that may confound the interpretation of how oestrous impacts vocal communication. To address this issue, the interactions between randomly paired adult male and female mice (9-21 weeks old; B6.CAST-Cdh23Ahl+/Kjn) were recorded for 30 minutes using an 8-channel microphone array that allowed us to estimate the location of the source and probabilistically assign vocal signals to individual animals. After oestrous state was determined using non-invasive lavage and cytological assessment of vaginal cells, interactions were recorded (proestrus, n = 13; estrus, n = 14; metestrus, n = 13; diestrus, n = 13). The vocal parameters of both males and females were quantified across each of the four different stages of the reproductive cycle. When comparing the number of USVs emitted during the different stages of the reproductive cycle for both males and females, significant differences were only observed in female mice (1-way ANOVA, $p < 0.02$). When independently examining the acoustic parameters of both male and female mice, we noticed a pronounced effect of reproductive stage on the start frequency, end frequency, mean frequency, duration, low frequency, high frequency, and how the frequency of the vocal signals changed over time (1-way ANOVA, all p values $< 10^{-3}$). For male mice, the bandwidth of the vocal signals also changed across different stages of the

reproductive cycle (1-way ANOVA, $p < 10^{-3}$). When examining reproductive behaviors, the percentage of sessions during which copulation occurred varied significantly (proestrus = 85%, estrus = 21%, metestrus = 8%; diestrus = 0%; $\chi^2_{(3,53)} = 28.5$, $p < 10^{-3}$), indicating the need to investigate context-dependent vocal expression. In summary, these results suggest that the characteristics of USVs produced by both male and female mice change across different stages of the reproductive cycle.

Disclosures: L.A. Meckler: None. **M.R. Warren:** None. **M.S. Spurrier:** None. **E. Roth:** None. **J.P. Neunuebel:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.07/MM6

Topic: F.01. Neuroethology

Title: Quantification of social communication in a mouse model of autism using a sound source localization system

Authors: *M. R. WARREN, J. P. NEUNUEBEL
Univ. of Delaware, Newark, DE

Abstract: Mice emit ultrasonic vocalizations (USVs) in a variety of behavioral contexts, such as courtship behaviors (Sales, 1972), aggressive encounters (Gourbal et al., 2004), and exploration (Mun et al., 2015). The utility of these signals, however, is still unknown, due to an inability to discern which animal is vocalizing during social interactions. To overcome this challenge, we used a system modified from Neunuebel et al. (2015) to assign vocal signals to individual animals. This was combined with an automatic behavioral classification program (Kabra et al., 2013) to elucidate the role vocal signals play in specific behavioral contexts. To this end, we attempted to leverage the power of a pre-established mouse model of autism that has been reported to exhibit both social and vocal deficits (Bader et al., 2011). Groups of wild-type (WT; 7 groups; 2 males and 2 females; 8-12 weeks of age) or autism-like mice (HET; 6 groups; 2 males and 2 females; 8-12 weeks) were allowed to interact freely for 5 hours. After recording, the following behaviors were examined: male approach male, approach female, chase male, chase female, fight, males circling each other, flee, and walk. The number of times that WT and HET mice engaged in each behavior was similar (Mann-Whitney U-test; all p-values > 0.07), although the durations of fight, male approach female, and male follow female were significantly longer for HET animals (1-way ANOVA, all significant p-values < 0.05). To investigate how animals vocalized in specific contexts, we quantified the vocal rate in each behavior. The vocal rate was significantly different across behaviors (2-way ANOVA, $F_{7,7804} = 28.66$, $p < 10^{-10}$), but not between the two genotypes (2-way ANOVA, $F_{1,7804} = 2.2$ $p > 0.1$). To determine the

relationship between particular types of USVs and specific behavioral contexts, we used a novel clustering algorithm to group vocal signals based on overall shape. For both WT and HET mice, our results revealed a significant interaction between behavior and vocal signal type (3-way ANOVA, $F_{99,579339} = 321.94$, $p < 10^{-10}$); however, no main effect of genotype was found (3-way ANOVA, $F_{1,579339} = 0$, $p > 0.9$). Thus, despite the fact that we found subtle behavioral differences in this previously described mouse model of autism as compared to WT animals, these results showed that context-dependent social communication is similar in these two groups. These findings indicate that assigning vocal signals to specific animals and examining context-dependent vocal expression may provide a more quantitative, comprehensive approach for assessing communication disorders in mouse models of autism.

Disclosures: M.R. Warren: None. **J.P. Neunuebel:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.08/MM7

Topic: F.01. Neuroethology

Support: NIH Director's Pioneer Award (DP1 OD006437)

NIDCD Intramural grant Z1A-000046-15

Title: Simultaneous whole-body plethysmography and vocalization recordings in the lysosomal-enzyme targeting pathway mouse model of stuttering

Authors: *T. D. BARNES[1], T. E. HOLY[2], D. DRAYNA[3]
[1]Anat. and Neurobio., [2]Neurosci., Washington Univ. Sch. of Med., Saint Louis, MO; [3]Natl. Inst. on Deafness and Other Communication Disorders, Bethesda, MD

Abstract: The genes and neurocircuitry that evolved to make human speech possible are largely unknown. One way to identify them is through studies of disorders of the system. However, there are few disorders of speech with an identified genetic source. One exception is stuttering, which has been linked to mutations in the lysosomal enzyme targeting pathway (LETP). The three genes in this pathway code for two enzymes that are responsible for labelling enzymes with a mannose-6-phosphate tag, which causes these enzymes to be directed to lysosomes. To learn more about how mutations in this pathway cause stuttering, we have developed a mouse model of stuttering. Specifically, we compared vocalizations of mice with a LETP mutation to those of wild type mice. One of the major phenotypic differences between the vocalizations of the two groups of mice was that the LETP mouse vocalizations had more frequent elongated pauses compared to their wild type littermates. In humans, one of the defining features of stuttering are

blocks in speech. During a block, a person is actively attempting to vocalize. Their breathing, as well as their speech, halts. It is unclear whether these previously identified elongated pauses in LETP mice are the equivalent of human blocks. Here, we show the results of a set of experiments utilizing whole-body plethysmography to determine the respiration patterns of mice as they vocalize. We show that the breathing data can be used to predict vocalizations with a high degree of certainty. With simultaneous acquisition of these data, we will be able to clearly determine the similarities and differences between elongated pauses in LETP mice and blocks in humans.

Disclosures: T.D. Barnes: None. **T.E. Holy:** None. **D. Drayna:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 157.09/MM8

Topic: F.01. Neuroethology

Title: c-Fos expression following alarm call perception by Richardson's ground squirrel

Authors: A. FREEMAN[1], J. F. HARE[2], *H. K. CALDWELL[3]
[1]Cornell Univ., Ithaca, NY; [2]Dept. of Biol. Sci., Univ. of Manitoba, Winnipeg, MB, Canada; [3]Dept. of Biol. Sci., Kent State Univ., Kent, OH

Abstract: While the neural mechanisms that underlie communication in birds are well studied, much less is known about how the brain works to interpret vocal signals in non-human mammals. In an attempt to address this deficit, we utilized female Richardson's ground squirrels (*Urocitellus richardsonii*) to determine what neural circuits were activated with vocal signals that are known to convey different types of information. Specifically, we played back chirp calls, which are emitted in response to airborne threats, or whistles, which are emitted in response to terrestrial threats. We then quantified immediate early gene activation (i.e. c-Fos) during the perception of these vocalizations and compared them to a no-vocalization control condition. Our analysis revealed that vocalization type affected the distribution and amount of c-Fos labelling. The majority of c-Fos activation was observed in the lateral septum, the nucleus accumbens, the thalamic nuclei, and the paraventricular nucleus of the hypothalamus (PVN). Modest expression was also detected in the ventromedial nucleus of the hypothalamus, the periaqueductal grey, the amygdalar nuclei, and the auditory cortex. Further, chirp and whistle calls had differential effects on c-Fos activation in the PVN, amygdalar nuclei, and periaqueductal grey, with chirps producing more activation than whistles and/or controls. We hypothesize that these differences may reflect the greater response-urgency associated with chirp vocalizations, which are emitted in the context of highly threatening avian predators. The extensive c-Fos labelling observed within the lateral septum of all groups in response to alarm calls may be due to the ability of

these squirrels to recognize alarm callers and hence represent social recognition memory, as demonstrated for other rodents, or may reflect stress and anxiety during alarm call perception. Taken together, our findings identify neural correlates of alarm call perception consistent with the purported function of those brain regions in rodents, and with the documented responses of alarm call receivers in nature.

Disclosures: A. Freeman: None. **J.F. Hare:** None. **H.K. Caldwell:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

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Program#/Poster#: 157.10/MM9

Topic: F.01. Neuroethology

Support: Sloan Foundation

NYSCF

NIH Director's New Innovator Award 1DP2DC016163-01

Klingenstein-Simons Fellowship

Pew Charitable Trust

HFSP

The Dana Foundation

Title: Encoding of learned vocalization in a developing mammalian brain

Authors: *M. C. ROSE[1], E. K. SAWYER[2], M. M. YARTSEV[1,2]
[1]Helen Wills Neurosci. Inst., [2]Bioengineering, Univ. of California Berkeley, Berkeley, CA

Abstract: Infants and children are expert **vocal learners**, capable of learning any of the myriad language sounds of the world from adults. Understanding how we achieve that proficiency is critical to our understanding of language as a whole. While vocal learning has been well studied at the behavioral and neural levels in an avian model - the songbird, the neural mechanisms that support vocal learning in the mammalian brain of humans remains largely unknown. In order to bridge this gap of knowledge we began to study this process in one of the only known non-human vocal learning mammals: **the bat**. We chose bats not only because of their mammalian brain organization but also for their impressive vocal repertoire and learning capabilities. Here we describe our initial efforts toward studying the brain mechanisms that support vocal learning in developing mammalian brain of Egyptian fruit bats (Rousettus aegyptiacus). We used light-

weight wireless electrophysiology recording methods to study the neural activity in the frontal motor cortices of juvenile bats engaged in **natural social interaction** with adults. We found that a large fraction of the recorded neurons exhibited highly selective neural responses during the production of learned acoustic signals but not during the production of innate acoustic signals, nor in response to auditory playback, suggestive of an exclusive **encoding of learned vocal elements**. Furthermore, we have begun to describe the changes in neural activity in the developing mammalian brain during the process of vocal learning. Combined, we will present the first evidence of cellular-resolution neural activity related to the production of learned vocalizations in the developing mammalian brain.

Disclosures: M.C. Rose: None. **E.K. Sawyer:** None. **M.M. Yartsev:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: NSF GRFP

Sloan Foundation

NYSCF

NIH Director's New Innovator Award (#1DP2DC016163-01)

Klingenstein-Simons Fellowship

Pew Charitable Trust

HFSP

Title: Towards a fully automated training system for studying vocal production learning in the mammalian brain of Egyptian fruit bats

Authors: *T. A. SCHMID[1], D. GENZEL[1,2], M. M. YARTSEV[1,2]
[1]Helen Wills Neurosci. Inst., Univ. of California Berkeley, San Francisco, CA; [2]Bioengineering, Univ. of California, Berkeley, Berkeley, CA

Abstract: Vocal learning is a complex motor production skill that leverages sensorimotor integration to facilitate imitation of an auditory template. Discovering the neural mechanisms underlying this ability in the mammalian brain is crucial to our understanding of how humans maintain proficiency in speech production learning throughout development and adulthood.

However, the absence of a tractable mammalian model system to probe this behavior has been a major obstacle to this end. Egyptian fruit bats are believed to acquire their social communication calls through the process of vocal learning and hence we propose to use this species of bat as a suitable mammalian model to tackle this issue. Two challenges interfere with performing high-throughput vocal production studies with bats in a controlled laboratory setting: variable call rates under experimental conditions, and the wide diversity of social vocalizations in the bat repertoire. To overcome these challenges, we developed a custom fully-automated operant behavioral setup using real-time audio processing and food reward to motivate vocal production in adult bats. First, we found that bats significantly increased their average call rate from less than 5 calls/hour to more than 35 calls/hour. Second, individual bats were trained to constrain their vocalizations to a single stereotyped call, thus allowing us to obtain a large sample of highly reproducible voluntary vocal production signals within a single behavioral session. Interestingly, individual bats converged onto different call types. Subsequently, we began working towards implementing the system to stimulate imitation in adult bats with modification of vocalizations through operant conditioning. Combined, this training system enables repeatable trials with direct control over social and contextual stimuli presented to the bat, and it opens the door for a systematic investigation of the neural mechanisms that support the production of learned acoustic signals in a vocal learning mammal.

Disclosures: **T.A. Schmid:** None. **D. Genzel:** None. **M.M. Yartsev:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: F.01. Neuroethology

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Sloan Foundation

NYSCF

NIH Director's New Innovator Award (#1DP2DC016163-01)

Klingenstein-Simons Fellowship

Pew Charitable Trust

HFSP

Title: Long-term and persistent vocal plasticity in adult bats

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Abstract: Bats are well-known for their extraordinary echolocation ability that allows them to aerially navigate in complete darkness. Less known is their diverse and complex vocabulary of social communication calls facilitating intraspecific information exchange. Underlying this capability is a vocal learning mechanism which necessitates a high-degree of vocal plasticity. Furthermore, bats live in socially tight-knit and acoustically noisy communities which most likely require long-term vocal plasticity to exist not in only in juveniles but in adulthood as well. The goal of this project was therefore to investigate for the existence of persistent vocal plasticity in adult Egyptian fruit bats (*Rousettus aegyptiacus*) in response to long-term noise exposure. We hypothesized that when exposed long-term to acoustic background noise, bats would adapt their vocalizations to minimize interference with the noise. By varying the spectral shape of the background noise, we specifically asked not only whether but also how bats would adapt their call parameters. Next, we examined the hypothesis that changes in call parameters emerging from the noise exposure would persist even after cessation of the noise. Our results indicate that not only do these bats modify distinct parameters of their vocalizations in response to the presented noise but that these changes persist even after cessation - suggestive of vocal plasticity. Furthermore, this change seems to be independent of social call type and group constellation – supporting a global adaptation of the produced sounds. The obtained results demonstrate persistent vocal adaptation in an adult bat and extensive vocal plasticity abilities of this bat species. The study supports their potentially important role as a model system for vocal production plasticity and learning.

Disclosures: D. Genzel-Wehrfritz: None. **J. Desai:** None. **E. Paras:** None. **M.M. Yartsev:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: PTDC/BIA-ANM/0810/2014

SFRH/BPD/121953/2016

Title: Developmental effects of early social complexity in adult zebrafish social traits

Authors: *M. C. TELES[1,2,3], C. GONÇALVES[1], R. F. OLIVEIRA[1,2,3]
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Abstract: The social brain hypothesis (SBH) posits that sociality is cognitively demanding, consequently driving cognitive evolution. Although this relationship between the complexity of the social environment and cognitive abilities has been shown in primates (group size as a measure of complexity, and relative brain size of the neocortex as an indicator cognitive skills), violations of this hypothesis have been reported when trying to generalize it across vertebrate taxa. Moreover, the use of the relative volume of a brain region of interest as a proxy of cognitive abilities has also been the focus of much debate, and recently the number of neurons rather that volume of brain tissue has been proposed to be the best proxy for computational power. Moreover, developmental effects on cognitive abilities and brain size have not been considered in the scope of the SBH. In the present work we used zebrafish to experimentally test the role of development in the SBH by raising individuals in environments with different social complexities, as defined by group size and stability, and phenotype them in adulthood for: i) sociality, ii) cognitive abilities, and iii) social competence at individual level. Brains were also collected and dissected into major regions and the number of neurons per region was analyzed. This study will establish a quantitative measure of the influence of social environment in the development of social skills at the behavioural level, and data on the neuronal numbers will shed light on the impact of environmental complexity on brain development.

Disclosures: M.C. Teles: None. **C. Gonçalves:** None. **R.F. Oliveira:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: NIMH Grant R33MH104188

Title: Forebrain control of reciprocal social interaction in the zebrafish

Authors: *S. J. STEDNITZ, E. MCDERMOTT, A. SEROKA, P. WASHBOURNE
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Abstract: Deficits in social engagement are diagnostic of autism, a developmental disorder with hereditary components. Genetically tractable animal models like the zebrafish (*Danio rerio*) could provide valuable insight into developmental factors underlying social impairments in the human population. This genetic-behavioral approach is a powerful tool in high-throughput

screens for potential therapeutics, but it is predicated on the ability to accurately and reliably quantify subtle behavioral changes. Characterizing local molecular and morphological phenotypes is similarly dependent on knowledge of the neuroanatomical correlates of social behavior. Here we present a novel, robust assay that reveals complex reciprocal social interactions in adult zebrafish dyads. Furthermore, we describe the forebrain contributions to sustaining social reciprocity, and identify a null mutation that impairs social interaction.

Disclosures: S.J. Stednitz: None. **E. McDermott:** None. **A. Seroka:** None. **P. Washbourne:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: NINDS NS23684

Fullbright

NSF GRFP

NRSA (IH)

NSF GFRP (CLB)

Whitman Fellowship, MBL

Title: Evolution of vocal circuits; analyses of hybrid song features in crosses between Xenopus laevis and Xenopus petersii

Authors: E. PEREZ[1,2], C. L. BARKAN[5], I. C. HALL[6], J. SEGARRA[1], S. M. WOOLLEY[3], *D. B. KELLEY[4]
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Abstract: African clawed frogs (*Xenopus*) are nocturnal and aquatic anurans; vocal signaling dominates social communication. During courtship, males produce a distinctive advertisement call with species-specific temporal and spectral features. These calls consist of trains of sound pulses (trills); each pulse consists of two simultaneous, dominant frequencies (DFs). Within the laevis clade, *X. laevis* and *X. petersii* calls include fast and slow trill components with distinct

DF2/DF1 ratios. Female *Xenopus* are more responsive to conspecific than to heterospecific calls: specifically sensitive to the spectral features of their own species' call, a difference that could contribute to pre-mating isolation and species divergence. We recorded advertisement calls from sexually mature *X. laevis/X. petersii* hybrids and analyzed the temporal and spectral features of their advertisement calls. Call duration, call period, fast trill duration and slow trill duration in male hybrids differ from both parental species but are closer to *X. petersii* than *X. laevis* while DF2, DF1 and DF2/DF1 are intermediate. To assess the spectral sensitivity of female hybrids, we are comparing auditory-evoked potentials (AEPs) elicited by synthetic two-tone sound pulses (dyads) - characteristic of both parental species and of hybrids - to shifted dyads. Ancient interspecific hybridizations have shaped the phylogenetic relationships of extant *Xenopus*. Divergence between *X. laevis* and *X petersii* in the duration of fast trill and call period are controlled by differences in intrinsic rhythmic features of vocal pattern generator within the parabrachial area of the rostral hindbrain. Both male and female hybrid offspring are inter-fertile, facilitating the generation of backcrosses and intercrosses in which vocal features and auditory sensitivity can be mapped to genomic loci. Thus analysis of vocal patterns in male and spectral sensitivity in female *X. laevis/X. petersii* hybrids may provide insights into mechanisms that drive the divergence of new species.

Disclosures: E. Perez: None. **C.L. Barkan:** None. **I.C. Hall:** None. **J. Segarra:** None. **S.M. Woolley:** None. **D.B. Kelley:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: NSF Grant IOS1557945

Title: Electroporation and viral vector technique to deliver transgenes into the vocal pathways of African clawed frogs

Authors: *A. YAMAGUCHI, P. RODRIGUES
Biol., Univ. of Utah, Salt Lake City, UT

Abstract: Understanding the neural mechanisms underlying behavior presents a formidable challenge requiring a well-chosen model system and sophisticated experimental tools. Vocalizations of the African clawed frog (*Xenopus laevis*) are an exceptionally well suited model system for this objective. In this species, a simplified mechanism of vocal production allows straightforward interpretations of neuronal activity with respect to behavior, and neural mechanisms of calling can be studied *in vitro* because fictive vocalizations can be elicited in the

isolated brain. Furthermore, the vocalizations of *Xenopus* are sexually differentiated, and rapid androgen-induced masculinization of female vocalizations provides an invaluable opportunity for determining how new behavior arises from existing neural circuits in response to steroid hormones. Despite these unique advantages, genetic tools that have revolutionized the field of neuroscience in recent years are largely not available. To overcome this obstacle, we explored techniques to express transgenes in the neurons of *Xenopus laevis*. Creating transgenic organisms is a labor-intensive, expensive, and a slow process. As an alternative, we applied acute transfection- and transduction-mediated gene expression technique to the *Xenopus* central nervous system. Specifically, we used targeted electroporation of plasmids and targeted injection of recombinant adeno-associated virus (rAAV), lentiviral vector system based on equine infectious anemia virus (EIAV), and recombinant vesicular stomatitis virus (rVSV) into the brains and cranial nerves of *X. laevis*. We discovered that the efficiency of the transfection and transduction depends on the age of the animals and the target location within the CNS. Electroporation was an effective method of delivering plasmids into the neurons in tadpoles, but when applied to the adult brains, the transgene expression was largely restricted to glial cells. Targeted injection of rAAV 2/9 into the adult brains of *X. laevis* resulted in highly variable transduction efficiency, and EIAV did not infect neurons of adult *X. laevis*. In contrast, rVSV with VSV glycoprotein injected into the forebrain and the midbrain of adult *X. laevis* yielded high and reliable transduction efficiency. However, injection of the same virus into the cranial nerves and brainstem (where the central vocal pathways are located) resulted in low yield. Our next goal is to enhance the VSV transduction efficiency in the brainstem by devising a better way to deliver the viral vector.

Disclosures: A. Yamaguchi: None. **P. Rodrigues:** None.

Poster

157. Communicating Vocally in Non-Avian Model Systems

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Topic: F.01. Neuroethology

Support: NSFC 31672305

NSFC 31372217

Title: Sexual dimorphism of attention network in anuran brain depends on biologic significance of sounds

Authors: *G. FANG[1], F. XUE[2], S. E. BRAUTH[3], Y. TANG[4]
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Sci., Chengdu, China; [3]Dept Psychology, Univ. Maryland, College Park, MD; [4]Chengdu Inst. of Biol., Chengdu, China

Abstract: The allocation of attention to biologically relevant signals plays a critical role in the reproductive strategies of both males and females and has been studied in many primates, other mammals and some bird species. In humans, attention allocation is modulated by the frontal cortex, and is reflected by predicable changes in specific components of the event-related potential (ERP). The present study used the ERP method to identify functional brain networks controlling attention modulation in an amphibian species, the music frog (*Babina daunchina*). Since all land vertebrates are derived from an amphibian stem, investigation of brain systems in amphibia can shed light on the evolution of attention modulation systems. Music frogs were used as subjects because males produce calls from underground nest burrows whose acoustic properties are modified by the resonant properties of the nests. Females can discriminate these changes and are attracted to males whose calls are produced from inside nests rather than from open fields. Both kinds of stimuli were presented to males and females while electroencephalographic (EEG) signals were recorded from the telencephalon and mesencephalon. By using Granger causal connectivity analysis, we identified putative brain networks connecting the telencephalon and midbrain based on EEG signals within the time window of ERP components. The results showed that the highly sexually attractive calls produced from inside nests resulted in the strongest functional connections; both ascending and descending connections involving the left telencephalon were stronger in males while those involving the right telencephalon were stronger in females. These results support the idea that frogs preferentially allocate neural attention resources to more attractive communication sounds and that sexual dimorphism of such attention modulation exists, presumably because the reproductive strategies of males and females differ.
Keywords: Auditory attention; brain network; Granger causal connectivity analysis (GCCA); sexual dimorphism, music frog.

Disclosures: G. Fang: None. **F. Xue:** None. **S.E. Brauth:** None. **Y. Tang:** None.

Poster

158. Neural Control of Social Interactions

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Topic: F.02. Behavioral Neuroendocrinology

Support: UCRF

PCLB

UConn IDEA Grant

Title: Influence of the social environment on female rats exploring a novel open field

Authors: *T. A. PIETRUSZEWSKI[1], N. HERNANDEZ[2], L. HORBAL[2], S. AHMED[2], R. TROHA[2], S. LEE[2], E. J. MARKUS[3]
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Abstract: Exploration of a new environment is an essential component of animal behavior, providing potentially crucial information regarding sources of food, shelter, and mates. The manner in which rats explore a novel environment has been examined previously using the open field task. Weiss and colleagues showed that male rats may explore familiar arenas differently in the presence of another male rat (Weiss et al., 2015). Recently we also showed that male rats explored a novel environment differently as individuals or pairs.
In the current study, we examined female rats during exploration of a novel environment. Three month-old female F344 rats (Harlan, IN), with free access to food and water were used for this experiment. Animals were paired for 7 days prior to and throughout testing. The open field exploration was assessed using a Plexiglas enclosure (70.5cm L X 70.5cm W) with a white plastic floor of the same area. During experimental trials, either one or two rats were placed in the southeast corner of the open field, and allowed to explore for fifteen minutes. The positions of the subjects within the open field were recorded using SMART-TW video multiple subjects tracking software (Panlab, Spain). The software allowed for tracking of multiple subjects simultaneously, each one physically marked with a different color.
Animals were placed in the novel environment either individually or in pairs. This was repeated the following day. This allowed for a comparison of exploration pattern of a novel environment (day 1) and a familiar environment (day 2). We will show to what degree exploring as an individual differs from pair exploration; importance of the pairs being cage-mates or strangers; as well as how these interact with the animal's stage of the estrous cycle.
Keywords: navigation, estrous cycle, exploration, spatial, navigation, stress
Funding: UCRF; PCLB; UConn IDEA Grant

Disclosures: T.A. Pietruszewski: None. **N. Hernandez:** None. **L. Horbal:** None. **S. Ahmed:** None. **R. Troha:** None. **S. Lee:** None. **E.J. Markus:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.02/MM18

Topic: F.02. Behavioral Neuroendocrinology

Title: Effects of lithium and high fat diet on sociability and anxiety in Black Swiss mice

Authors: A. V. CUSHMAN, N. L. ARRUDA, R. R. GELINEAU, I. K. MONTEIRO DE PINA, M. J. MARONI, K. M. CAPRI, *J. A. SEGGIO
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Abstract: Bipolar disorder is characterized by behaviors including extreme irritability and aggressive behavior. In the United States approximately 5 million people have been diagnosed with bipolar disorder and 2.6% of people worldwide are diagnosed with bipolar disorder. A common therapy for patients exhibiting these symptoms is treatment with lithium which has been shown to stabilize manic behaviors. However, environment plays a role on the efficacy of this treatment as variables such as consumption of a poor diet which has been shown to exacerbate these symptoms. This study examines the effects of lithium and high fat diet on social and explorative-like behaviors in Black Swiss mice, a model for bipolar mania. Black Swiss/CR mice were housed individually in standard 12:12 lighting conditions and were given ad libitum access to either regular chow (RC) or high fat diet (HFD) and were given either water or 10 mM lithium drink. Behavioral tests were conducted including a light:dark (LD) Box, social test and open field to measure anxiety levels and sociability of the animals. Weekly measurements of food and liquid intake were conducted as well as measurements of BDNF and vasopressin in the frontal lobe and hypothalamus following completion of the study. Black Swiss mice that consumed lithium exhibited an increase in distance traveled and center zone time in the open field test indicating they were more explorative and less anxious, which was corroborated by the observation of increased levels of BDNF in the frontal lobe but not the hypothalamus. High fat diet did not alter anxiety or explorative behaviors or affect BDNF within the frontal lobe or hypothalamus. Additionally, lithium produced increased explorative behaviors during the LD box by exhibiting increased rearing and distance traveled. However, mice consuming high fat diet exhibited increased approaches and biting behaviors, indicating increased aggression towards the social mouse, and decreased levels of vasopressin within the hypothalamus. Lithium produced no effect on sociability markers. These results indicate that lithium treatment can improve anxiety-like symptoms within a bipolar mouse model, but was ineffective in treating increased aggressive social behaviors due to high fat diet.

Disclosures: A.V. Cushman: None. **N.L. Arruda:** None. **R.R. Gelineau:** None. **I.K. Monteiro De Pina:** None. **M.J. Maroni:** None. **K.M. Capri:** None. **J.A. Seggio:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Topic: F.02. Behavioral Neuroendocrinology

Support: JSPS KAKENHI Grant Number 15K04180

JSPS KAKENHI Grant Number 16K04419

Title: Social enrichment enhances rats' memory span of social, but not object, recognition

Authors: *M. TOYOSHIMA, M. SUGITA, Y. ICHITANI, K. YAMADA
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Abstract: The social environment is thought to have a strong impact on cognitive functions. A large social network, for example, could prevent age-related cognitive decline in humans, and housing a number of cage mates improve rodents' performance in memory tasks. In the present study, we investigated whether social enrichment could affect rats' memory ability using the "Different Objects Task (DOT)," in which the levels of memory load can be modulated by changing the number of objects to be remembered. In addition, we applied the DOT to a social recognition task using unfamiliar conspecific juveniles instead of objects. Wistar-Imamichi male rats were housed in one of the three different housing conditions after weaning (postnatal day (PND) 21): single, standard (3 per cage) or social-enriched (10 per cage) conditions. The object and social recognition tasks were conducted on PND 63. In the sample phase, the rats were allowed to explore a field in which 3, 4, or 5 different, unfamiliar stimuli (juveniles or objects) were presented. After a 5-min delay period, they were again placed in the field in which one of the sample stimuli was replaced by a novel stimulus, and their exploration behavior to these stimuli was analyzed. In the social recognition task, the rats of the single condition were able to discriminate the novel juvenile from the familiar ones only under the condition in which 3 different juveniles were presented; social-enriched rats managed to recognize the novel juvenile even under the condition in which 5 different juveniles were presented. On the other hand, in the object recognition task, both singly-housed and social-enriched rats were able to discriminate the novel object from the familiar ones under the condition in which 5 different objects were presented. These results suggest that social enrichment can enhance social, but not object, memory span.

Disclosures: **M. Toyoshima:** None. **M. Sugita:** None. **Y. Ichitani:** None. **K. Yamada:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Program#/Poster#: 158.04/MM20

Topic: F.02. Behavioral Neuroendocrinology

Support: Case Western Reserve University Rodent Behavioral Core

Title: Are balb/c mice less social? a detailed analysis of social process in two inbred mouse strains

Authors: *H. ARAKAWA
Dept. of Res. Admin., Case Western Reserve Univ., Cleveland, OH

Abstract: BALB/c mice, an inbred strain, are considered less social in the sociability test, which has been referred as a model of social withdrawal relevant to an autism-like phenotype. The behavioral process of sociability (defined as a tend to seek social contact) has received little attention in the related literatures. The present series of experiments aimed to evaluate the sequence of social contacts between male mice of C57BL/6 (B6) and BALB/c (BALB) strains. In the sociability test, both B6 and BALB mice revealed a moderate level of approach to the stimulus mouse as an assessment behavior during the first 5 min. In the second 5 min of the test, B6 mice tended to spent time in the proximity of the stimulus mouse, while BALB mice stayed near an empty bin. When confronted with social odorants or stimulus mice, BALB mice showed distinct approach and investigation as B6 mice did, which indicates no impairment in social discrimination or approach behavior in BALB mice. With detailed ethological analysis of social interaction, BALB mice displayed differential patterns of investigation compared to B6 mice, in which BALB mice persist in frontal (face) investigation to the stimulus mice, while B6 mice stick to back (anogenital) investigation. A neuropeptide oxytocin and serotonin (5-HT) appear to modulate these processes via changing social signals. Social cues emitted by mice (probably via anogenital area) that were injected with oxytocin or 5-HT induced approach behavior in signal recipient mice. Odor cues collected from mice that received an injection of oxytocin or 5-HT increased approach preference in B6 recipient, but not BALB mice. The interactive feature of social signals between male mice illustrates that social cues facilitating approach preference are eliminated via the 5-HT --> oxytocin pathway, and BALB mice are not capable of recognizing such amicable signals during social contact. Therefore, BALB mice as well as B6 mice exhibit distinct social approach/investigation to an unfamiliar conspecific and are able to recognize social features such as age and familiarity. Subsequently, B6 mice receive amicable signals from the stimulus mice resulting in increased approach preference, while BALB mice fail to receive the signals and thus lacking approach to conspecifics. These data also revealed a conceptual issue in the sociability test paradigm that is frequently employed as an autism-like behavioral model.

Disclosures: H. Arakawa: A. Employment/Salary (full or part-time):; Case Western Reserve University School of Medicine.

Poster

158. Neural Control of Social Interactions

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Program#/Poster#: 158.05/MM21

Topic: F.02. Behavioral Neuroendocrinology

Support: Helse Nord grant PFP1295-15

Title: The effects of perinatal SSRI exposure on behavior during adulthood

Authors: *R. HEIJKOOP[1], D. J. HOUWING[2], J. D. OLIVIER[2], E. M. SNOEREN[1]
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Abstract: The use of selective serotonin reuptake inhibitors (SSRI) during pregnancy has increased tremendously. Serotonin plays a key role during development and disturbances have been linked to altered social behavior and neurodevelopment. Most studies investigating the effects of perinatal SSRI use, however, focus on the juvenile phase and use limited test set-ups. Therefore, this study investigated the behavioral effects on adult offspring in a seminatural environment in which rats live in groups and can freely express their full repertoire of behavior. The responses to a stressful white-noise presentation were also examined.
Mothers received daily oral gavage of 10 mg/kg fluoxetine or vehicle from gestational day 0 until postnatal day 21. The female and male offspring (n=10 each) were weaned on day 21 and behaviorally tested at the age of 3 months. Offspring was housed in groups of 8 rats (4 females and 4 males) in the seminatural environment for 8 days and behavior recorded. The females were ovariectomized and treated with 18 µg/kg estradiol benzoate (day 5) and 1 mg progesterone (day 7). Behavior on day 4 and 7, 30 minutes before and 10 minutes during white-noise presentation, was observed and analyzed.
On day 4, fluoxetine-exposed female offspring showed less locomotor activity, less non-social exploration behavior and more passivity compared to control females. In addition, females showed lower levels of social activity: they played less and spent less time sniffing others. Interestingly, the fluoxetine-exposed male offspring did not show different behaviors compared to control males, except for more self-grooming behavior. During the white-noise, no behavioral differences were found between fluoxetine-exposed and control offspring. The behavioral effects were no longer visible on day 7, when the females were hormonally primed. Only fluoxetine-exposed male rats showed more locomotor activity. This was probably caused by a higher level of sexual pursue compared to control males.
These results suggest that SSRI use during pregnancy can disrupt adult social behavior of female offspring, while it does not seem to affect male offspring. The hormonal state of the female seem to be an important regulator in this effect. A stressful life-event, on the other hand, did not alter behavioral responses in fluoxetine-exposed rats. Together, these results indicate a sex difference in the sensitivity to serotonin disturbances during development.

Disclosures: **R. Heijkoop:** None. **D.J. Houwing:** None. **J.D. Olivier:** None. **E.M. Snoeren:** None.

Poster

158. Neural Control of Social Interactions

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NARSAD Independent Award 2015

Pennsylvania Commonwealth 4100072545 (CURE 2016)

Title: Prefrontal D1 dopamine signaling controls social behaviors in mice

Authors: *B. XING, W.-J. GAO
Neurobio. & Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Social behaviors, including social motivation, social recognition, and social hierarchy, depend on dopamine signaling. The prefrontal cortex (PFC) has been suggested to play a top-down control of social behaviors via its rich dopaminergic inputs from the midbrain ventral tegmental area. However, it remains unknown how prefrontal dopamine influences social behaviors. Here, we demonstrate a specific role for dopamine D1 receptor (DRD1)-expressing neurons in the medial prefrontal cortex (mPFC) in the regulation of social behaviors. Social interaction selectively increases the c-fos expression in DRD1-expressing neurons in the mPFC. These exhibit different electrophysiological (action potential, h current, as well as synaptic activity in terms of AMPAR- and NMDAR-mediated currents), morphological (dendritic branching and cell body size) properties from those cells that are activated by aggression. Additionally, chemogenetically inhibition of D1 neurons decreases male-male social interaction but increases aggression without affecting the anxiety levels and locomotor activity. We also evaluate the effects of inhibiting prefrontal DRD1 neurons on social motivation, social recognition, and social hierarchy, through three-chamber test, habituation-dishabituation test, and tube test, respectively. Moreover, chemogenetic inhibition of prefronal-nucleus accmubens (NAc) prejection is sufficient to decrease normal social interaction, recapitulating the effects of mPFC D1 inhibition. These results suggest that the prefrontal D1 signaling regulates normal social behaviors through connections with the NAc.

Disclosures: B. Xing: None. **W. Gao:** None.

Poster

158. Neural Control of Social Interactions

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Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: Nucleus accumbens dopamine D1-type receptors mediate social learning but not food intake in male and female mice

Authors: *R. MATTA, M. J. RUSSELL, D. J. TESSIER, N. BASS, E. CHOLERIS
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Abstract: Social learning is an adaptive form of learning that allows animals to acquire information from others. The neurobiological mechanisms underlying social learning are not well understood. With systemic drug treatments using dopamine (DA) receptor antagonists, our lab has previously shown that DA D1-type receptors regulate social learning, whereas DA D2-type receptors regulate feeding behavior in the social transmission of food preferences (STFP) in mice (Choleris et al., 2011). The brain regions underlying these effects are slowly being investigated. Many limbic brain regions including the hippocampus and nucleus accumbens (NAc) receive direct dopaminergic projections from the ventral tegmental area. With dorsal hippocampal infusions we showed that a D1-type receptor antagonist blocks social learning in both males and females (Matta et al., 2017), whereas dorsal hippocampal infusions of a D2-type receptor antagonist blocks social learning in female but not male mice (Matta et al., 2016). The NAc is implicated in both social behavior and individually acquired food preferences in rodents. Hence, in this study we investigated the involvement of NAc DA D1-type receptors in the STFP. We infused the DA D1-type receptor antagonist SCH23390 (at 1, 2, & 4 μg/μL) bilaterally into the NAc shell of adult male and female CD-1 mice. Infusions were 15 minutes before a 30 minute social interaction where mice had the opportunity to learn a food preference through a social interaction with a same-sex mouse. Results show that the lowest dose of SCH23390 (1 μg/μL) blocked social learning in male mice, and the highest dose of SCH23390 (4 μg/μL) blocked social learning in female mice. Furthermore, the effects on social learning could not be explained by generalized changes in feeding behavior, since SCH23390 did not significantly affect total food intake in either males or females. Possible effects of drug treatment on various behaviors during the social interactions (including oronasal investigation), and possible effects on olfactory discrimination are being assessed. We are also highlighting sex differences and possible effects of the estrous cycle.

Disclosures: R. Matta: None. **M.J. Russell:** None. **D.J. Tessier:** None. **N. Bass:** None. **E. Choleris:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.08/NN2

Topic: F.02. Behavioral Neuroendocrinology

Support: APS IOSP Undergraduate Summer Research Fellowship IOS-1238831

NIH Grant MH070712

Title: Dopamine enhances female zebra finch preference for male song

Authors: *L. E. EISENMAN[1], M. BURNS[2], N. F. DAY[3], S. A. WHITE[3], M. J. COLEMAN[4]
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Abstract: The neural mechanisms by which the nervous systems generates affiliative behaviors is not well understood. Work in the prairie vole, a monogamous rodent, has shown that dopamine acting through the dopamine 2 receptor (D2R), is important for pair-bond formation. Monogamy is more common in birds than in mammals, so comparing mechanisms of affiliative behavior between birds and voles is critical to identify conserved neural underpinnings. Thus, we are examining the neurochemical basis for pair-bond formation in zebra finches, *Taeniopygia guttata*. Song is an honest signal of fitness, so female selection of a 'good song' is an important strategy in partner selection. For this reason, we used song preference to begin to understand the role of DA on mate selection and pair-bond formation. We used an operant testing paradigm equipped with infrared sensors to trigger song playbacks of either the mate's song or a novel song. Females that were housed with a single male for >2 weeks (pair-bonded females) preferred their mate's song over another male's song. Unpaired females were paired with a male for 24 hours during which they were treated twice with a drug (see below) or saline. We found that D2Rs are both necessary and sufficient to induce a song preference. A systemic injection of a D2R agonist (quinpirole), but not a D1R agonist ((±)-SKF-38393), significantly increased the female's preference for a male's song with whom she was housed for 48 hours while receiving the drug, indicating that activation of D2Rs is sufficient to induce a song preference. Injection of the D2R antagonist (raclopride) blocked song preference in pair-bonded females but birds injected with the D1R antagonist (SCH-23390) retained a preference for their partner's song, indicating that D2Rs are necessary for song preference. These data show that D2 receptors are important for pair-bond formation in finches, and suggest that there are similar mechanisms for affiliative behaviors in birds and voles. We are currently quantifying the differences in levels of D1R and D2R in pair-bonded, unpaired, and birds that receive the D2 agonist to begin to determine the neural mechanisms and circuitry involved in pair-bond formation.

Disclosures: **L.E. Eisenman:** None. **M. Burns:** None. **N.F. Day:** None. **S.A. White:** None. **M.J. Coleman:** None.

Poster

158. Neural Control of Social Interactions

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Program#/Poster#: 158.09/NN3

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH R01NS082179

Title: Testosterone synthesis in the female brain during auditory processing

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Abstract: Steroids are synthesized in the brain and act as neuromodulators to regulate important biological functions such as reproduction, cognition or sensory processing. Songbirds are a tractable model to study the cellular/molecular mechanisms that regulate the production and the sensory coding of learned vocalizations. In zebra finches, estradiol is rapidly synthesized in the auditory cortex (caudomedial nidopallium; NCM) in response to conspecific songs. In both males and females, estradiol is produced in the brain via aromatization of androgens like testosterone, and the aromatase enzyme is densely expressed in NCM. Local estradiol levels within NCM are rapidly elevated when males and females hear song, and local increases in estradiol rapidly enhance the auditory responses of NCM neurons. However, the mechanisms by which estradiol elevations occur within NCM remain unknown. Here, we hypothesize that local estradiol rises during song exposure via an increase in local levels of the androgen substrate, testosterone. The enzyme that regulates testosterone synthesis, 3β-HSD, is present and active in the zebra finch NCM and can be acutely regulated by environmental stimuli. In this study, we assessed testosterone fluctuations within NCM during song exposure using in vivo microdialysis. These fluctuations were assessed in females because of their lower peripheral testosterone levels and higher 3β-HSD activity in NCM as compared to males. In adult females, we observe that local levels of estradiol, but not testosterone, were significantly elevated in the NCM during song playback. By contrast, when the local production of estradiol was concurrently blocked by an aromatase inhibitor, we then observe a massive (≥500%) song-evoked increase in testosterone levels within NCM. Furthermore, no significant changes in plasma testosterone were observed in females during song exposure, indicating that the song-evoked peak in NCM testosterone resulted from local brain synthesis and not peripheral fluctuations. Ongoing experiments using an androgen synthesis inhibitor will further test this mechanism of local testosterone production in the brain. Together, these results strongly suggest that elevations in NCM estradiol levels

associated with song processing are mediated by a local increase in testosterone production. To our knowledge, this is the first direct evidence showing that testosterone can be synthesized within the brain. As testosterone is currently viewed as a male-typical hormone, these results suggest that its production in the female brain could be critical for fundamental brain functions and behaviors.

Disclosures: C. De Bournonville: None. **L. Remage-Healey:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Program#/Poster#: 158.10/NN4

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF GRFP Grant DGE-16-44869

Title: Immediate early gene activation throughout the social behavior network in response to dynamic changes in social status

Authors: *C. WILLIAMSON, W. LEE, I. KLEIN, J. P. CURLEY
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Abstract: Understanding the neural mechanisms of dynamic social behavior requires both complex social behavior analysis as well as rigorous neurobiological techniques. Our lab investigates the social relationships of groups of adult outbred CD1 male mice (n=12) living in a large, complex vivarium. The aggressive (fighting, chasing, mounting) and subordinate (fleeing, freezing) behaviors between mice are recorded during focal sampling observations (2-5 hours per day, >1000 behavioral events per vivarium) that start daily at the onset of the dark/red light cycle. Previously, our lab has demonstrated that male CD1 mice living in these groups of 12 form significantly linear dominance hierarchies and that social rank is associated with differential gene expression throughout the brain. Here, we show that removal of the alpha male from the group leads to flexible behavioral changes in the remaining mice, with the beta male rapidly rising to alpha status and exerting high levels of aggression on all other individuals in the system. In this study, we examine c-fos immunoreactivity throughout the brain in order to determine which brain regions within the social decision making network are activated when an individual is recognizing this social change, integrating social information, and behaving in a contextually appropriate manner while undergoing social transition. We show that the infralimbic and prelimbic regions of the prefrontal cortex are differentially activated in response to this change in social status. Further, we present preliminary data demonstrating the behavioral consequences of selectively inhibiting this region of the prefrontal cortex using the DREADD system. This research highlights a novel behavioral paradigm where we are able to study

complex, socially competent behaviors as well as provides insight into the neural mechanisms of social behavior in large, socially dynamic groups.

Disclosures: **C. Williamson:** None. **W. Lee:** None. **I. Klein:** None. **J.P. Curley:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: D.05. Olfaction and Taste

Support: Samsung Scholarship

Title: Effect of relative social rank within a social hierarchy on neural activation in response to familiar or unfamiliar social signals

Authors: *W. LEE[1], H. DOWD[2], C. NIKAIN[1], E. YANG[1], J. P. CURLEY[1]
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Abstract: Living in a social hierarchy shapes the physiology of individuals as well as their perception of social cues from others according to their own relative social status. We have previously shown that alpha males living in social hierarchies invest vast resources in scent-marking and the production of major urinary proteins (MUPs) and serve as an honest signal of the alpha status. Here, we identified brain regions involved in the perception of specific social cues in urine that are relevant to showing appropriate social behaviors in different social contexts. We housed adult outbred CD1 male mice (n=12) in a large vivarium constructed to resemble the wild habitat of the progenitors of laboratory mice. We reconfirm the previous finding that groups of 12 male mice living in these vivaria form stable linear dominance hierarchies in which each animal can be ranked individually. We show that animals living in the social hierarchy are able to flexibly change their social behaviors appropriate to different social contexts. We demonstrate brain-region specific activation throughout the social brain network of c-fos protein immunoreactivity throughout the social behavior brain network as mice are exposed to urine from familiar-alpha males, unfamiliar-alpha males, familiar-subordinate males or unfamiliar-subordinate males. Further, we demonstrate that animals vary in the degree of neural activation to the same social cue as they differ in their relative social ranks. Within brain regions we found significant differences across different social ranks or social cues, we performed double-label fluorescent immunohistochemistry to identify cellular types of the neurons that were activated in response to the social cues. This study emphasizes the importance of studying the neurobiological underpinnings of social dynamics within an ethologically relevant behavioral paradigm.

Disclosures: **W. Lee:** None. **H. Dowd:** None. **C. Nikain:** None. **E. Yang:** None. **J.P. Curley:** None.

Poster

158. Neural Control of Social Interactions

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Program#/Poster#: 158.12/NN6

Topic: F.02. Behavioral Neuroendocrinology

Support: Jeffress Memorial Trust Award

Title: Behavioral and neural control of social dominance in mice

Authors: *R. P. WATERS[1], W. D. STAHLMAN[2]
[1]Biol., [2]Psychology, Univ. of Mary Washington, Fredericksburg, VA

Abstract: Laboratory mice are social animals that exhibit specific patterns of behavior during social interactions that result in the formation of dominance hierarchies. Reciprocally, a mouse's hierarchical rank influences the temporal and behavioral characteristics of its ethology. These behavioral characteristics are strongly influenced by central neuropeptides expressed in brain regions that control appetitive and stress related behaviors, and understanding how these neurobiological systems influence, and are influenced by, social interactions allows us to build a holistic picture that relates physiology and behavior to evolutionary fitness. Voluntary wheel running (VWR) is a model of aerobic activity that is spontaneously and robustly performed by mice in the laboratory. This activity has profound effects on the behavior and neurophysiology of mice, with extensions into social interactions. This study explores the connections between ethology, social rank, and neuropeptides, and how these traits are influenced by physical activity. We performed a high resolution, high fidelity assessment of social homecage behavior using radio-frequency identification (RFID) tags to constantly track the position and movements of mice in a social colony (five mice per colony). Additionally, we used RFID gated tubes to allow selective access to a running wheel, which allowed us to assess the influence of VWR on behavioral patterns and social rank. Finally, we assessed neuropeptide levels in brain regions that respond to appetitive and aversive stimuli and that are associated with social behavior.

Disclosures: **R.P. Waters:** None. **W.D. Stahlman:** None.

Poster

158. Neural Control of Social Interactions

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant RO1NS034950-21

Title: Androgens control distinct social behaviors: Evidence from genetically tractable cichlid fish

Authors: *B. A. ALWARD, *B. A. ALWARD, A. T. HILLIARD, S. A. JUNTTI, R. D. FERNALRD
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Abstract: Given their remarkable diversity in social behaviors, cichlid fish provide an opportunity to investigate the fundamental molecular and neural mechanisms controlling behavior. For example, the African cichlid fish *Astatotilapia burtoni* has been studied extensively to elucidate the neural and hormonal mechanisms of social behavior. In *A. burtoni*, dominant (D) male fish maintain territories through aggressive interactions and court females, while non-dominant (ND) males do not perform these behaviors. D males have higher levels of androgens such as testosterone (T) and 11-ketotestosterone (11-KT; a fish specific androgen) compared to ND males. Androgen signaling is required for the performance of many behaviors associated with dominance in D males. When given the opportunity, ND males rapidly attempt to establish a territory and court females, a process that has been called “social ascent”. On the day of ascent, these males show enhanced T and 11-KT levels that are not different than D males. However, it is not known what role androgens play in the regulation of behavior during social ascent. We investigated this question using a social ascent paradigm. Two days before the opportunity to socially ascend, ND males were injected with an androgen receptor (AR) antagonist, cyproterone acetate (CA) (ASC+CA). Ascending (ASC), stable ND, and stable D male fish were included as controls. We show that while ASC+CA and ASC males on the day of social ascent increase aggressive interactions to levels seen in D males, only ASC fish increase courtship interactions. Therefore, androgen signaling regulates courtship but not aggressive behaviors on the day of social ascent in male *A. burtoni*. However, it is still unclear how androgens regulate social behaviors in *A. burtoni*. For instance, as a result of genome duplication *A. burtoni* possess two AR subtypes encoded by two separate genes, *ar1* and *ar2*. Hence, we will continue our investigations on how androgen signaling regulates social behavior in *A. burtoni* using fish with mutated AR genes. To this end, we have used CRISPR-Cas9 genome editing technology to generate *A. burtoni* that possess loss-of-function (i.e. frameshift indels or large deletions) alleles encoding *ar1* and *ar2*. Investigating the role played by the distinct ARs in the

regulation of social behavior using mutant *ar1* and *ar2* fish will provide insight into the fundamental molecular mechanisms of social behavior and its evolutionary trajectory.

Disclosures: B.A. Alward: None. **A.T. Hilliard:** None. **S.A. Juntti:** None. **R.D. Fernalrd:** None.

Poster

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Program#/Poster#: 158.14/NN8

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Grant 1257162

Title: Comparative studies of affiliation, aggression, and selectivity in monogamous and promiscuous voles

Authors: *N. S. LEE[1], K. E. FREITAS[2], N. L. GOODWIN[3], A. K. BEERY[2,1]
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Abstract: Relationships between same-sex peers are central to life in social groups. The prairie vole (*Microtus ochrogaster*) is widely studied for its reproductive pair bonds, but individuals also demonstrate selective preferences for familiar same-sex peers. A related species, the meadow vole (*Microtus pennsylvanicus*), is not socially monogamous, but lives in groups during the winter, and displays affiliative behavior toward peers in short day lengths (SD). Aggression also plays a role in the social organization and mating system of each vole species. Prior research has established that prairie voles display more aggressive behavior toward same-sex conspecifics after pair bonding with opposite-sex partners. Meadow vole aggression varies by season: in the summer (long days, LD) breeding season, females are aggressive and territorial, while males and females in winter (SD) form communal huddling groups. Day length is sufficient to mediate changes in peer affiliation, namely selective, long-lasting preference for a same-sex conspecific. We examined the effects of species (meadow vs. prairie), day length (SD vs. LD), and housing (solo- vs. pair-housed) on aggressive behavior toward an unfamiliar same-sex peer. Female voles underwent a social interaction test, in which a focal vole was placed in a testing chamber with a stranger. The frequency of aggressive interactions (lunges, bites, chases, offensive rears), latency to aggressive bouts, and duration of aggressive behaviors were measured. Latency to attack was significantly lower for SD prairie than SD meadow voles. Meadow voles housed in SDs exhibited more social interaction than in LDs, and pair-housed meadow voles showed more social and investigative behaviors than solo-housed meadow voles. We also examined the effects

of species, day length, and sex on affiliative behavior toward a same-sex partner. Voles underwent a 3hr partner preference test in which focal voles roamed freely in a 3-chambered apparatus with the partner tethered to one end and a stranger to the other. Time in each chamber, time alone, time huddling with each of the tethered voles, and activity were measured. All groups exhibited partner preferences for their cage-mate, and formed partner preferences for new same-sex partners upon re-pairing. There were no sex or day length differences in prairie vole peer affiliation. Prairie voles preferred their original partners more strongly than meadow voles, and were more aggressive upon re-pairing. Thus, meadow vole sociality may depend on social tolerance, characterized by their lower aggression and selectivity, whereas prairie vole sociality is highly selective and is maintained by aggression.

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Poster

158. Neural Control of Social Interactions

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Topic: F.02. Behavioral Neuroendocrinology

Support: Canadian Institutes of Health Research (CIHR)

Ontario Mental Health Foundation

Title: Stranger Danger! Ghrelin Receptor Signalling in the VTA and its role in social approach and social interaction

Authors: *S.-B. PARK[1], S. KING[1], S. DE SANTE[2], G. CULKA[3], G. PARODI[1], L. HYLAND[1], R. KHAZALL[1], J. ZIGMAN[4], B. WOODSIDE[5], A. ABIZAID[1]
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Abstract: Ghrelin is a gut-derived peptide hormone associated with feeding, energy balance, reward, and the stress response. In the brain, ghrelin receptors (GHSR) are expressed in both hypothalamic and extra hypothalamic regions including the ventral tegmental area (VTA), a region that is important for modulating reward-seeking behaviours. Previously in our lab, we have demonstrated that GHSR knockout (GHSR KO) mice exhibit social deficits in comparison to GHSR wild type (WT) mice. Furthermore, peripheral administration of the GHSR antagonist JMV2959 caused social behaviour deficits in mice compared to those injected with saline. Given that activation of GHSR in the VTA is associated with increases in reward-seeking behaviours, and that activation of dopamine cells in this region is associated with increased expression of

pro-social behaviors, we hypothesized that blocking GHSR in the VTA would result in decreased social behaviors. To test this hypothesis, we measured social interaction behaviors in mice that were implanted with osmotic minipumps delivering either saline or JMV2959 (5ug/day) unilaterally into the VTA (AP-2.92, ML +/- 0.7, DV -4.5) for a period of 3 weeks. Results showed that, like GHSR KO mice, mice receiving chronic infusions of JMV2959 into the VTA took longer to approach stranger mice, and spent less time investigating these mice ($p< 0.05$). In a second study, mice inserted with a loxP-flanked transcriptional blocking cassette (TBC) preventing the transcription of GHSR, and their WT littermates were micro infused with an adeno-associated virus (AAV) packaged with either green fluorescent protein (GFP) or a fusion of GFP and CRE-recombinase (4.44e9 GC/ml) into the VTA (AP-2.92, ML +/- 0.7, DV -4.5) to rescue expression in this region. As expected, TBC infused GHSR null mice receiving the control virus showed a longer latency to approach strangers, whereas reactivation of the GHSR in the VTA reduced the latency to approach a stranger and increasing the amount of sniffing and stretching towards stranger mice ($p< 0.05$). These results support the idea that ghrelin receptor signalling in the VTA is important for elicitation of pro social behavior and disruptions in ghrelin signalling in the VTA may be associated with social anxiety.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: FAPESP

CAPES/PROEX

CNPq

Title: Effects of hormonal therapy on aggressive behavior and central nervous system in an animal model of perimenopause

Authors: *M. M. SCAFUTO[1], N. PESTANA-OLIVEIRA[2], R. M. DE ALMEIDA[3], R. O. G. CAROLINO[4], J. A. ANSELMO-FRANCI[5]
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Abstract: Perimenopause is the transitional period between fertile life and menopause, marked by numerous changes in mood and behavior that are associated with hormone imbalance and increased risk of anxiety and mood disorders. Irritability is one of the top ranked complaints for up to 70% of women in perimenopause, which very often can be serious enough to disrupt their lives and every day interactions. Thus, the aims of this study were to evaluate the effects of hormone therapy in the aggressive social behavior as well as in the content of serotonin (5HT) and noradrenaline (NA) on the prefrontal cortex (PFC) in a recent described ovarian-intact perimenopausal rat model. To induce perimenopause, 28 day-old female Wistar rats were treated with 4-vinylcyclohexene diepoxide (VCD) s.c. for 15 consecutive days .Control rats were treated with corn oil (Oil). Fifty-nine days after the first injection of VCD/Oil rats received a subcutaneous capsule containing placebo (groups Oil+PL and VCD+PL); estradiol (VCD+E2); progesterone (VCD+P4) or a combination of both sex steroids (VCD+E2P4). Sixteen days later, rats were submitted to the Social Instigation (SI) and Resident-Intruder (RI) test, in which offensive aggression behaviors were analyzed (clinch attack, lateral threat, keep down, bite, upright posture, chase and move toward) followed by the Open Field (OP) test for locomotor activity analysis (session 1). Four days later, rats were submitted to a second set of the same tests (session 2). Immediately after the session 2, the rats were decapitated, the brain removed and the (PFC) dissected to measure 5HT and NA by HPLC-ED. For analysis, ONE-WAY ANOVA was performed, followed by the Newman Keuls test, with significance when $P < 0.05$. Ours results showed that animals in periestropause are more aggressive than the control and the three sort of hormonal therapies can prevent it. There was no difference in the locomotor activity among groups, which means it did not affect the RI test. Periestropausal rats showed a decreased concentrations of 5HT which was not affected by the hormonal therapies. In conclusion progesterone and estradiol, alone or associated might to be effective to attenuate irritability, impulsiveness and aggressive behavior in perimenopausal women acting though other brain areas than PFC.

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Poster

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Topic: F.02. Behavioral Neuroendocrinology

Support: KU University Graduate Fellowship

Title: Behavioral phenotype following social defeat in prairie voles (Microtus ochrogaster)

Authors: *M. C. TICKERHOOF, A. P. SWOPES, L. H. HALE, A. S. SMITH
Dept. of Pharmacol. & Toxicology, Univ. of Kansas, Lawrence, KS

Abstract: The prairie vole (*Microtus ochrogaster*) is a highly social rodent species that has come into popularity as a model for social affiliation and attachment. While the behavioral and neurochemical effects of being an aggressor have been characterized in this species, the response to losing an aggressive confrontation has not been studied. The goal of this study was to establish a model of social defeat stress in prairie voles and to characterize the behavioral phenotype as a result of this stressful life event. Both male and female prairie voles were subjected to a short period of physical aggression from an aggressive same-sex conspecific, followed by a longer threat session of exposure to non-physical aggressive behavior. Following this, a series of behavioral tests was performed in order to characterize the effects on in-group and out-group social interaction, anxiety-like behaviors, and depressive-like behaviors. Our results show that male prairie voles subjected to repeated social defeat avoid subsequent investigation of novel same-sex conspecifics but not novel objects, and females show a statistical trend in the same direction. However, no difference in behavior is observed between control and defeated voles in generalized anxiety-like behavior as measured during an elevated plus maze test. These findings indicate that defeat in an aggressive confrontation in the prairie vole leads to an alteration in normal social functioning by inducing a social avoidance response but may not affect anxiety-like behavior outside of a social context. Ultimately, this highlights the potential use of social defeat stress in the prairie vole as a model for social anxiety and impaired social interaction.

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Poster

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Strategic Research Programme in Diabetes at Karolinska Institutet

Title: The role of the ventral premammillary nucleus in intermale mouse aggression and hierarchy

Authors: *A. S. STAGKOURAKIS[1], G. SPIGOLON[1], P. WILLIAMS[1], J. PROTZMAN[2], G. FISONE[1], C. BROBERGER[1]
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Abstract: Conspecific intermale aggression is a behavior observed across the animal kingdom. Aggression helps the individual achieve social dominance, which, in turn, promotes survival by optimizing access to resources and reproductive success. Specific subsets of neurons in hypothalamic nuclei drive attack, aggression-seeking behaviour and aggression-associated reward. The ventral premammillary nucleus (PMv) has been associated with reproduction and social behaviors. Aggression, which embodies the antagonistic expression of social behaviour, has, however, received little attention as a consequence of PMv activity. Following the behavioural expression of aggression the immediate early gene, c-fos, indicative of neuronal activation, was expressed in PMv neurons expressing the dopamine transporter (DAT; "PMv-DAT cells"), which represent ca. one-third of all neurons in the nucleus. Using the resident-intruder paradigm and other behavioural models, we show that optogenetic activation of PMv-DAT in male mice leads to social investigation and attack in an escalating manner with a reward component, while silencing of PMv-DAT neurons inhibits initiation of attacks and terminates ongoing attacks. In whole-cell patch clamp recordings, PMv-DAT neurons in slice preparations were found to exhibit membrane properties conducive to reverberatory discharge that, combined with intra- and internuclear re-entrant excitatory connectivity, provide a network framework for the persistence of attack behavior. Acute optogenetic manipulation of PMv-DAT activity during a single intermale hierarchy challenge, leads to a long-lasting switch of the dominance relationship to a conspecific. These results identify the PMv as an organizing node in the neural circuit underlying behaviors that determine intermale social rank.

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Poster

158. Neural Control of Social Interactions

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Program#/Poster#: 158.19/NN13

Topic: G.03. Emotion

Support: Autism Speaks Grant #9699

NIH Grant R25MH071584

NIH Grant T32MH014276

Title: Regulation of aggressive behavior in mice by hippocampal alpha7 nicotinic receptors

Authors: *A. S. LEWIS[1], S. T. PITTENGER[1], Y. S. MINEUR[1], P. H. SMITH[2], M. R. PICCIOTTO[1]
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Abstract: Impulsive aggression can complicate severe forms of neuropsychiatric disorders that occur across the lifespan, worsens outcomes, and can lead to recurrent hospitalization or involvement with the criminal justice system. For some patients, aggressive behavior is refractory to current non-pharmacological and pharmacological treatment approaches. We reason that improved understanding of the neural circuitry underlying aggression might enhance the development of more effective and specific therapeutics. We recently reported that systemic nicotine dose-dependently reduces aggression in resident-intruder tests with a social isolation model of aggression in male mice. This anti-aggressive, or "serenic" effect of nicotine was blocked by an antagonist of α7 nicotinic acetylcholine receptors (nAChRs), but not by an antagonist of heteromeric nAChRs, and was recapitulated by systemic administration of GTS-21, an α7 nAChR partial agonist (Lewis et al., 2015). The goal of the present study was to better understand where α7 agonists act in the mouse brain to induce a serenic effect. We focused on the hippocampus, where α7 nAChRs are highly expressed. Previous studies have demonstrated preferential localization to GABAergic inhibitory interneurons in dentate gyrus (DG), and α7 activation can strongly inhibit local excitatory granule cells. In male C57BL/6 mice, we found that the immediate-early gene (IEG) Arc in the DG was significantly increased after resident-intruder interactions as compared to home cage controls, and this activation was reduced by GTS-21 treatment. DG Arc staining correlated with IEG staining in multiple other brain regions important for aggression. These data suggest DG activity might bidirectionally gate initiation of aggressive behavior. Consistent with our hypothesized mechanism that α7 activation inhibits DG activity to reduce aggression, low-dose picrotoxin (0.1 mg/kg), a GABA-A receptor antagonist, blunted the serenic effect of GTS-21. Finally, shRNA knockdown of α7 in the hippocampus increased baseline aggression and eliminated the serenic effect of nicotine and GTS-21. These experiments demonstrate the importance of hippocampal α7 receptors for the serenic effects of nicotine and an α7 partial agonist, and suggest that the balance of hippocampal excitation and inhibition might be a more general mechanism regulating aggressive behavior.

Disclosures: A.S. Lewis: None. **S.T. Pittenger:** None. **Y.S. Mineur:** None. **P.H. Smith:** None. **M.R. Picciotto:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.20/NN14

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH/NCI 1 R21 CA202745-01A1

NIH/NCI 1 R01 CA170249

Title: Elevated aggressive behavior in mice with thyroid-specific PRKARAa and global EPAC1 gene deletion

Authors: *K. L. RUSSART[1], D. HUK[2], R. J. NELSON[1], L. S. KIRSCHNER[2]
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Abstract: Genetic modification of mice is an important tool for investigating human disease and behavior. Thyroid-specific knockout of *Prkar1a*, which encodes the type1a regulatory subunit of protein kinase A (PKA), induces follicular thyroid cancer (FTC) in 40% of animals and a hyperthyroid phenotype. A potential therapeutic target for FTC is exchange protein directly activated by cAMP (Epac), an intracellular receptor, in addition to PKA, that mediates the effects of cAMP. Therefore, $Prkar1a^{-/-}$ mice were crossed with $Epac1^{-/-}$ mice, generating *Tpo-Cre;*$Prkar1a^{flox/flox}$*;*$Epac1^{-/-}$ mice. In addition to therapeutics, this mouse model presents the opportunity to investigate the role of both genes in behavior, both independently and as a reciprocal effect in the double KO. Both hyperthyroidism and EPAC proteins have been linked independently with behavioral abnormalities. In humans with an over-active thyroid, comorbidity with affective disorders and ADHD is often reported. Furthermore, hyperthyroid rodents also display affective disorders as well as locomotor deficits. Deletions of *Epac* alter anxiety-like behaviors, activity levels, depressive-like responses, and learning. Here, we characterize the behavioral phenotypes of three genotypes, $Prkar1a^{-/-}$, $Epac1^{-/-}$, and $Prkar1a^{-/-}$*;*$Epac1^{-/-}$ using a barrage of sensorimotor, memory, affective behavior, compulsive behavior, pain tolerance, and aggression tests. Our study indicates thyroid-specific deletion of $Prkar1a^{-/-}$ in combination with *Epac1* knockout increases responsiveness, vigilance, and aggression. These behaviors are likely driven by hyperthyroidism induced by thyroid-specific deletion of *Prkar1a*.

Disclosures: D. Huk: None. **R.J. Nelson:** None. **L.S. Kirschner:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.21/NN15

Topic: G.03. Emotion

Support: NIGMS Grant GM119962

Title: Dorsal raphe regulation of aggression via the medial orbitofrontal cortex and the medial amygdala

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Abstract: ABSTRACT
Violence and aggression are serious concerns for modern society. Current therapeutic strategies are limited due to a lack of understanding about the neurological mechanisms underlying aggression and the environmental triggers that cause it. A number of studies have demonstrated that the dorsal raphe (DR), a major serotonin (5-HT) nucleus, is a critical regulator of social behaviors like aggression, however the precise contribution of the DR to these behaviors has remained elusive. In this study we show that the DR inhibits aggression via a circuit involving the medial orbital frontal cortex (MeOC) and the medial amygdala (MeA), two major loci underlying aggression. We performed circuit mapping analysis and found that DR neurons densely project onto the MeOC and MeA. c-Fos labeling revealed that optogenetic activation of the DR increases activity in those brain regions. To determine how these putative aggression circuits regulate, we optogenetically stimulated or silenced neurons of the DR as well as their projections onto the MeA and MeOC. Silencing of the DR and it's projections onto the MeOC inhibited aggression during a social interaction test. Interestingly, stimulating DR projections onto the MeA also inhibited aggression. Direct optogenetic stimulation of glutamatergic neurons at the MeOC and MeA inhibited aggression, as did stimulating projections from the MeOC to the MeA, suggesting a trisynaptic circuit underlying aggression regulation. Finally, to determine whether 5-HT neurons of the DR regulate this inhibitory aggression circuit, we present a novel FRET based 5-HT sensor for use *in vivo* to discern 5-HT induced activity related to aggression. This study will help elucidate the role of the DR and 5-HT in regulating aggression, and provide possible therapeutic targets in the fight against pathological aggression and violence.

Disclosures: **J. Nordman:** None. **X. Ma:** None. **Z. Li:** None.

Poster

158. Neural Control of Social Interactions

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Program#/Poster#: 158.22/NN16

Topic: F.02. Behavioral Neuroendocrinology

Support: FAPESP # 2013/20602-5

Title: 24 months follow-up after amygdala lesion in refractory aggressive patient

Authors: *F. V. GOUVEIA[1], C. HAMANI[2], E. T. FONOFF[3], H. BRENTANI[4], R. M. C. B. MORAIS[5], S. P. RIGONATTI[4], M. J. TEIXEIRA[3], R. C. R. MARTINEZ[1]
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Abstract: Four refractory aggressive patients where submitted to functional neurosurgical procedures for the partial bilateral removal of the amygdala. The literature indicates that the bilateral ablation of this nuclei reduce the patient aggressive behavior, nevertheless, the neurobiological mechanisms of this reduction are unknown. In this sense, the aim of this work is to evaluate four refractory aggressive patients (1 female, 3 male) before and 1, 12 and 24 months after surgery. The levels of: Thyroid-stimulating hormone (TSH), free T4, T3, Cortisol, Luteinizing Hormone (LH), Estradiol, Prolactin, Progesterone, Testosterone, and Sex hormone-binding globulin (SHBG) where measured, and the Overt Aggression Scale (aggressive behavior), Agitated Behavior Scale (motor agitation) e SF-36 (quality of life) scales where applied. Our results indicate a reduction in aggression after surgery and an increase after 24 months without reaching the same level as before. Furthermore, there is a positive correlation between agitation and aggression in all patients and between testosterone levels and aggression in male patients. No alteration in hormone levels was observed. We conclude that the partial removal of the amygdala results in the reduction if the aggressive behavior and that, in male patients this behavior is related to testosterone levels.

Disclosures: F.V. Gouveia: None. **C. Hamani:** None. **E.T. Fonoff:** None. **H. Brentani:** None. **R.M.C.B. Morais:** None. **S.P. Rigonatti:** None. **M.J. Teixeira:** None. **R.C.R. Martinez:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Program#/Poster#: 158.23/NN17

Topic: F.02. Behavioral Neuroendocrinology

Support: The Paul and Maxine Frohring Foundation

Title: Coat color modulates behavioral responses to predator threat in the eastern gray squirrel, Sciurus carolinensis

Authors: *T. J. KOEHNLE
Biol., Hiram Col., Hiram, OH

Abstract: In mammals, expression of certain melanocortin receptor ligands is correlated with both dark pigmentation and increased stress resistance and higher levels of aggression. Though many studies of captive and laboratory animals have explored this pleiotropic interaction between melanocortin receptor expression and behavior, relatively few studies of animal personality have occurred in free-living wild animals. This playback study focused on the antipredator behavior differences between melanistic and gray morphs of the eastern gray squirrel (Sciurus carolinensis) in Hiram, Ohio. Vigilance, tail flagging, freezing, and escape behaviors were recorded in response to digital playback of an American robin call, a chickadee call, a car alarm, a buzzer, or one of two different red-tailed hawk calls. All squirrels exhibited increased antipredator behavior after hearing increasingly threatening stimuli. Consistent with prior findings in other species with color polymorphism, gray morphs were more likely to escape after hearing a threatening call. Melanistic morphs were also more tolerant of novel stimuli. A growing body of evidence indicates it is possible to study pleiotropic effects of genes in free living animals.

Disclosures: T.J. Koehnle: None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.24/NN18

Topic: F.02. Behavioral Neuroendocrinology

Support: This was was supported by the Military Operational Medicine Research Program, US Army.

Title: Underwater trauma and predator exposure cause distinct neuroendocrine and behavioral response profiles in rats

Authors: D. E. ALTMAN[1], S. GAUCHAN[1], K. D. CRAVEDI[1], C. V. VUONG[2], J. C. SOUSA[2], *N. L. MOORE[1]
[1]Ctr. for Military Psychiatry and Neuroscience, Behavioral Biol. Br., [2]Ctr. for Military Infectious Dis. Research, Drug Metabolism and Distribution, Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: The physiological response in rats to a life-threatening event can be acutely measured using neuroendocrine and behavioral markers. Change in expression of these interrelated measures may vary across molecules and behaviors, and outside factors including the type of stressor or the phase in circadian cycle may also influence observed changes. Many rodent models of traumatic stress have examined response to acute stressors, but a comprehensive interrelated molecular and behavioral approach is less commonly used. The aim of the present study is to describe the subacute effects of traumatic stress exposure and recovery using a panel of neuroendocrine markers, and to compare those alongside acute and long lasting behavioral responses such as exploratory behavior and acoustic startle response, over the circadian cycle. Rats were exposed to either underwater trauma (UWT) or predator exposure (PRED). Repeated behavioral tests (exploratory behavior on the elevated plus maze, acoustic startle) were conducted across 5 individual time points over a 7 day period. Additionally, serial blood samples were collected over 10 time points across the circadian cycle from yoked stress-exposed cohorts that were not behaviorally tested. Neuroendocrine markers were quantified from serum using LC-MS or ELISA, their expression patterns were analyzed over time, and then compared against behavioral responses at corresponding time points. Preliminary data show differential responses between UWT and PRED across the experimental timeline, and distinct response timelines for the different measures collected. These results suggest that different stressors produce unique response profiles relevant to the specific threat.
Supported by the Military Operational Medicine Research Program, US Army Medical Research and Materiel Command.
Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, NRC Publication, 2011 edition. All procedures were reviewed and approved by the WRAIR Institutional Animal Care and Use Committee, and performed in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International.

Disclosures: **D.E. Altman:** None. **S. Gauchan:** None. **K.D. Cravedi:** None. **C.V. Vuong:** None. **J.C. Sousa:** None. **N.L. Moore:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.25/NN19

Topic: G.03. Emotion

Support: NSF Grant 1149446

Title: Social isolation-induced stress: Influence on the medial prefrontal cortex neurons in african naked mole-rats

Authors: *N. L. GAGGI[1], D. MCCLOSKEY[2]
[2]Psychology, [1]Col. of Staten Island, CUNY, Staten Island, NY

Abstract: The African naked mole-rat (*Heterocephalus glaber*), one of only two eusocial mammalian species, provides a unique opportunity to study how the brain processes complex social behavior. Previous work in our laboratory, and by researchers in the field, has demonstrated a strong prevalence of affiliative behavior in this species, with colony members spending most of their time in the presence of colony mates. In the present study, we sought to understand the consequences of a restriction from affiliative behavior, through social isolation, on stress physiology and neuron morphometry. The focus was on the medial prefrontal cortex, an area which mediates social and emotional processing, which is sensitive to social stress in other species. Six naked mole-rats of ages ranging from 2 months to 6 years were extracted from their colony and singly housed. A yoked control for each animal was maintained in the colony housing environment. After three weeks, dendritic length and spine density were measured in 3-D reconstructed Golgi-stained neurons in layers II/III of the medial prefrontal cortex. Social isolation increased fecal cortisol levels over the three-week period. While dendritic length did not vary significantly between groups, spine density showed a trend towards significance. In addition, social condition (isolated or control) served as a better predictor for both dendrite length and spine density than age or sex. Together, these data provide the first evidence of social interaction to physiology and brain organization in this species.

Disclosures: **N.L. Gaggi:** None. **D. McCloskey:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Program#/Poster#: 158.26/NN20

Topic: G.03. Emotion

Support: NSF Award 1149446

Title: Hippocampal neuropeptide-y in relation to social behavior in the African naked mole-rat

Authors: C. DUNNE-JAFFE[1], B. CUKOVIC[1], T. DZEDZITS[2], *D. P. MCCLOSKEY[1,3]
[1]Dept of Psychology and Program in Developmental Neurosci., City Univ. of New York, Staten Island, NY; [2]Grad. Ctr. at CUNY, New York, NY; [3]CUNY Neurosci. Collaborative, Grad. Ctr. of CUNY, New York, NY

Abstract: The African Naked Mole-Rat (Heterocephalus Glaber) is a fossorial rodent with a eusocial cooperative breeding organization. This species adapts well to a laboratory housing environment and continues to demonstrate innate, ethologically relevant colony maintenance behaviors even after generations of captive breeding. We have previously identified a division of labor among colony workers, with larger animals participating more in colony maintenance behaviors in and around the nest chamber (defense, nest building, tunnel excavation) and smaller animals participating more in digging and foraging behaviors distal to the nest (in a sand digging task). We have also previously identified individual differences in expression patterns of neuropeptide Y (NPY) in the hippocampus and cortex among worker animals. Work in eusocial insects, such as honeybees, has identified NPY as an important biomarker for caste differences. Here, we measured whether division of labor can account for differences in NPY expression. Animals from a captive naked mole-rat colony (n=47) were implanted with radio frequency identification transponders (RFID) and antennae were placed throughout the housing environment. The RFID network was used to track individual participation of all colony members in colony maintenance and distal foraging tasks presented over a 10-day period. Animals were selected based on performance of these tasks, and hippocampal NPY expression was evaluated with confocal microscopy of immunohistochemically-labeled tissue. In general, animals showed an unusual pattern of expression, with NPY staining restricted to what appear to be axonal filaments in the stratum radiatum region of CA1. Images were classified based on the extent axonal NPY-like expression by two experimenters blind to the treatment conditions. Consistently the larger nest-oriented animals demonstrated low hippocampal NPY-like expression compared to the smaller foraging-oriented animals. Therefore, our results support that NPY may be a useful biomarker for worker caste in mammalian eusocial groups.

Disclosures: C. Dunne-Jaffe: None. **B. Cukovic:** None. **T. Dzedzits:** None. **D.P. McCloskey:** None.

Poster

158. Neural Control of Social Interactions

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 158.27/NN21

Topic: F.02. Behavioral Neuroendocrinology

Support: NSF IOS-1457108

Cornell University Center for Vertebrate Genomics

Cornell Neurobiology and Behavior

Title: Sociogenomics of preoptic area in alternative reproductive morphs of a vocal fish

Authors: J. TRIPP[1], N. Y. FENG[2], *A. H. BASS[1]
[1]Cornell Univ., Ithaca, NY; [2]Yale Univ., New Haven, CT

Abstract: Appropriate regulation of social behavior is essential for an animal's reproductive success. Teleost fish species that engage in alternative reproductive tactics (ARTs), such as the plainfin midshipman (*Porichthys notatus*), are useful models for studying behavioral plasticity because they provide extreme examples of intrasexual variation in reproductive mechanisms, and social behavior in general. Male midshipman fish develop into one of two alternate morphs. Larger type I males build and defend nests; acoustically court females; and provide parental care. Type II males lack these characters and instead reproduce by cuckolding at the nest of a type I male. Some type I males that do not have a nest of their own resort to cuckolding tactics, but type II males never engage in building and defending a nest or in acoustic courtship, even in the absence of other males. Cuckolding type I males provide a special opportunity to better understand how social behavior is regulated by short-term plasticity related to behavioral state versus long-term developmental factors. We used RNA-sequencing to create a transcriptome of the preoptic area (POA) of spawning male midshipman, including nesting type I males, cuckolding type I males, and cuckolding type II males. We focused on the POA due to its pivotal role in the regulation of social behavior and its importance as a center of neuro-hormonal integration in the brain. Unexpectedly, there were nearly three-fold more transcripts differentially expressed across behavioral state than across male morphs. 147 genes were differentially expressed when comparing all cuckolding (types I and II) to nesting (type I) males. Of these, 32 were upregulated in cuckolders and 115 were upregulated in nesters. Of the 55 transcripts that were differentially expressed when comparing all type I males to all type II males, 18 were upregulated in type I males and 37 were upregulated in type II males. We found several genes related to hormone signaling that were differentially expressed across morph and behavior groups. Of note, genes showing differential expression included those related to the stress response - precursors of urocortin and corticotropin-releasing hormone, and to parental

care - the teleost homologue of the oxytocin receptor and a precursor of galanin peptide. These results provide candidate genes for the regulation of social behavior and alternative mating tactics, and suggest that POA gene expression is driven more by behavioral state than developmental morph trajectory.

Disclosures: J. Tripp: None. **N.Y. Feng:** None. **A.H. Bass:** None.

Poster

158. Neural Control of Social Interactions

Location: Halls A-C

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Topic: F.02. Behavioral Neuroendocrinology

Support: Christopher Newport University Summer Scholar Award to H. Kay (2016)

Title: Using behavior tracking to examine Zebrafish (Danio rerio) responses to live and simulated social stimuli

Authors: *A. J. VELKEY[1], T. BETTS[2], H. KAY[2], I. TILMONT[2], B. PITTS[2], B. KERNS[2], R. BOLAND[2], K. POND[2], J. HOOD[2], K. WIENS[2]
[1]Psychology, [2]Christopher Newport Univ., Newport News, VA

Abstract: Zebrafish (*Danio rerio*) share a considerable amount of biological similarity with mammals as they possess identical or homologous neurotransmitters, hormones, and cellular receptors. Zebrafish are fecund in captivity, demonstrate a wide variety of behavioral responses, and develop rapidly. Zebrafish serve as an excellent model organism for the comparative study of vertebrate social behavior. One characteristic response of zebrafish is their tendency to aggregate in shoals. While zebrafish behavioral research has developed rapidly over the past twenty years, shoaling behaviors are not as well characterized, leaving the results of certain studies difficult to interpret. Few investigators have systematically explored shoaling behavior as it relates to the fidelity of the social stimuli used in such experiments.
The purpose of the current study is to observe shoaling responses and determine whether zebrafish show a preference towards a shoal containing live conspecifics over a shoal of simulated conspecifics. *Danio rerio* performed an open-tank, free swim task while responses were recorded and analyzed with Ethovision XT 10 to identify location preferences and swimming patterns in response to a set of 3 stimuli; a live shoal, a moving model, or video-playback of a live shoal. Because zebrafish are increasingly common in behavioral studies, determining their preference for live conspecifics can be useful for studies of their social behavior.
Analyses indicated that zebrafish have a distinct preference for the live conspecific option, and this preference was notably stronger when the subject is tested with a shoal of live conspecifics

vs. the video-recorded shoal. These results indicate that zebrafish in the current study spent more time in proximity to a live shoal rather than a recorded shoal or moving models. The present study reveals that zebrafish can distinguish between live conspecifics and other moving stimuli, and that they prefer live conspecifics over these lower-fidelity options indicating that the type of social stimuli is important for future study of social & behavioral responses in zebrafish.

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Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

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Program#/Poster#: 159.01/NN23

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant RR003037

Training Grant GM060665

Training Grant NS080686

NIH DIDARP Grant DA012136

Title: Rapid changes in mushroom spines and synaptic markers in hippocampus CA1 following acute estradiol to male rats

Authors: *B. CARVAJAL[1], J. A. AVILA[1,2], A. ALLIGER[1], R. ZANCA[1,2], P. A. SERRANO[1,2], V. N. LUINE[1]
[1]Psychology, Hunter Col., New York, NY; [2]The Grad. Center, CUNY, New York, NY

Abstract: Hippocampal dendritic spine density rapidly increases following estradiol (E_2) treatment, but the types of spines and synaptic markers altered have received little *in vivo* investigation. We assessed effects of E_2 on density of immature (stubby and filopodial) and mature (long thin and mushroom) spines in tertiary, apical dendrites of CA1. In addition, PSD-95, marker of synapses, and GluA2, AMPAr subunit of glutamate receptor important for memory, were measured in the spines. Castrated male rats received 20ug/kg of E_2 or vehicle and sacrificed 30 and 120 min post injections. Following Golgi-Cox impregnation, spines were detected and counted using IMARIS XT parameters based on relative spine neck and head relationships. PSD95 and GluA2 were visualized in the spines using fluorescent IHC methods under the confocal microscope. Stubby spines did not change as a consequence of E_2 treatment. Density of long-thin spines showed a significant reduction 30 min following E_2 compared to vehicle ($p=0.04$) while mushroom spines showed a significant increase 120 min following E_2

treatment compared to vehicle (p=0.03). GluA2 levels in stubby or long thin spines did not change with E_2 treatment, but 30 min following E_2, GluA2 levels within filopodial spines were decreased compared to vehicle and to 120 min after E_2 treatment (p=0.005 and 0.006, respectively). Mushroom spine GluA2 levels significantly increased 120 min following E_2 treatment compared to vehicle (p=0.027). PSD95 levels within stubby, filopodia and long-thin spines were not altered by E_2, however, levels within mushroom spines significantly increased 120 min following E_2 treatment compared to vehicle (p=0.038). GluA2/PSD95 colocalization levels in mushroom spines significantly increased 120 min following E_2 treatment compared to 30 min after E_2 (*p=0.036) and levels were not altered in other spines. Results show that E_2 increases mature mushroom spine density in CA1 of the hippocampus 120 min after treatment and that these spines may be establishing functional synapses since PSD95 and GluA2 levels are also increased in the mushroom spines. Since E_2 increases memory consolidation at this dose and time interval in gonadectomized male and female rats, the current results suggest that rapid maturation of GluA2 containing mushroom spines provide one mechanism contributing to estradiol's ability to enhance learning and memory.

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Poster

159. Hormones and Cognition: Estrogens

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.02/NN24

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant 400212

Title: Rapid estrogenic enhancements of learning and memory within the hippocampus of female mice: A role for membrane-bound receptors

Authors: *T. KUUN[1], S. ARMSTRONG[2], R. BRAR[2], M. KLEMENS[2], E. CHOLERIS[2]
[1]Univ. of Guelph, Cambridge, ON, Canada; [2]Univ. of Guelph, Guelph, ON, Canada

Abstract: Estrogens are known to play an important role in long-term changes in learning and memory through genomic mechanisms (Nilsson et al., 2001). More recently, research has begun to uncover the rapid mechanisms of estrogen-mediated changes in learning and memory, which can occur in minutes (Woolley, 2007). Systemic injections of 17β-estradiol (E2), one of the most potent naturally produced estrogens, produce enhancements of learning and memory on a rapid 40-minute timeframe in ovariectomized female mice (Phan et al., 2012). Social recognition, object recognition and object placement learning, or the abilities to discriminate between conspecifics, objects or object spatial positions, are all enhanced within this timeframe, which is

widely considered too rapid to be caused by the aforementioned long-term genomic mechanisms of estrogen action. These rapid enhancements are also produced by bilateral infusions of E2 to the hippocampus (Phan et al., 2015), however the specific mechanisms involved in these learning enhancements within this brain region remain unknown. This study aims to use E2 conjugated with a bovine serum albumin (BSA-E2) molecule to learn more about the starting point of these mechanisms. The large BSA molecule prevents the E2 from passing through the cellular membrane and from binding to intracellular receptors, as it normally would (Taguchi et al., 2004). Therefore, the use of BSA-E2 allows us to study the effects of E2 on membrane-bound estrogen receptors, without interaction with nuclear or cytosolic estrogen receptors, to help elucidate the binding location and starting point of these rapid effects. The study uses the aforementioned 40-minute social recognition, object recognition and object placement learning paradigms, all similar in format, involving habituation phases and a final test phase where one of the stimuli is replaced by a novel stimulus to test for recognition learning. Due to the innate inclination for mice to preferentially investigate novelty, investigative behaviors can be analyzed to determine whether recognition learning has occurred. Enhancements of learning and memory were reproduced, suggesting that the rapid effects of estrogens in the hippocampus responsible for these enhancements of learning and memory within mice are mediated, at least in part, by membrane-bound receptors. This knowledge exposes an important first step in the pathways responsible for the rapid estrogenic enhancements of learning and memory within the hippocampus, which provides a source for further exploration of these mechanisms in the future. Supported by NSERC.

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Poster

159. Hormones and Cognition: Estrogens

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Program#/Poster#: 159.03/NN25

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC 400212

Title: The effects of PI3K inhibition on the rapid facilitation of social recognition by estrogens or estrogen receptor agonists in the dorsal hippocampus in female mice

Authors: *P. A. SHEPPARD[1], A. LUMSDEN[1], I. WATSON[2], K. SELLERS[3], D. P. SRIVASTAVA[3], E. CHOLERIS[1]
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Abstract: In addition to their delayed/long-lasting effects on gene transcription, rapid effects of estrogens on learning and memory have been repeatedly shown. Facilitation of social recognition occurs within 40 minutes of systemic administration of 17β-estradiol (E2), as well as estrogen receptor α (ERα) and G-protein coupled estrogen receptor (GPER) selective agonists (PPT and G-1 respectively), but not an estrogen receptor β (ERβ) agonist (DPN) in female mice (Phan et al, 2011; 2012; Gabor et al, 2015). Intra-dorsal hippocampal administration of E2, PPT, or G-1 facilitates social recognition (Phan et al, 2015; Lymer, 2015). In addition, systemic administration of E2, PPT, or G-1 increases dendritic spine density in the dorsal hippocampus (Phan et al, 2011; 2012; Gabor et al, 2015). The mechanisms of action of these rapid effects are not well understood. A role for estrogenic actions on cell signaling cascades underlying synaptic plasticity and dendritic spine dynamics is likely (Sellers et al., 2015). Inhibitors of the phosphoinositide-3 kinase (PI3K)/Akt pathway block rapid actions of E2 on object memory consolidation (Fan et al., 2010) and modulate dendritic spine density, size, and complexity (Kumar et al., 2005). Furthermore, PI3K signaling is involved in hippocampus-dependent learning tasks (Cui et al., 2010) and downstream activation of mTOR (Cui et al., 2010; Fortress et al., 2013; Winter et al., 2011). Whether the PI3K pathway is also involved in rapid estrogenic facilitation of social recognition in the hippocampus is unknown. First we infused (0.5μL/side, 0.2μL/min) PI3K inhibitor LY294002 (0.5, 1, 5, 10, 100 or 250ng/side) into the dorsal hippocampi of ovariectomized female mice 15min prior to testing for social recognition. Doses 10ng/side and above blocked social recognition. We then infused into the dorsal hippocampus LY294002 at 5ng/side, which does not affect social recognition by itself, to investigate only the PI3K-dependent effects of 6.81pg E2, 19.322pg PPT, or 41.228pg G-1 (per side) – doses shown to rapidly facilitate social recognition in a difficult version of the social recognition paradigm which is completed within 40 minutes of estrogen/ER agonist/vehicle administration, thus assessing rapid effects of estrogens.

Disclosures: P.A. Sheppard: None. **A. Lumsden:** None. **I. Watson:** None. **K. Sellers:** None. **D.P. Srivastava:** None. **E. Choleris:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.04/NN26

Topic: F.02. Behavioral Neuroendocrinology

Support: University of Wisconsin-Milwaukee College of Letters and Sciences

UWM Research Foundation Research Growth Initiative grant

Title: The role of actin polymerization in GPER-mediated hippocampal memory enhancement in female mice

Authors: *J. KIM, J. C. SCHALK, W. A. KOSS, K. M. FRICK
Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: We previously reported that dorsal hippocampal (DH) infusion of the G-protein coupled estrogen receptor (GPER) agonist, G-1, mimicked the beneficial effects of 17β-estradiol (E_2) on object recognition and spatial memory consolidation in ovariectomized female mice (Kim et al., 2016, JNeurosci, 33:3309-3321). We also showed that a bilateral DH infusion of E_2 significantly increases dendritic spine density in the DH within 30 minutes (Tuscher et al., 2016, JNeurosci, 36:1483-1489). However, effects of GPER activation on dendritic spine density are unclear. Thus, the present study examined effects on DH dendritic spine density of bilateral DH infusion of G-1. G-1 significantly increased the number of dendritic spines on apical dendrites of CA1 pyramidal neurons in the DH. We next examined cellular mechanisms regulating G-1 induced spinogenesis. Because hippocampal spine remodeling depends on the reorganization of the actin cytoskeleton, we examined the effects of G-1 on the actin-binding protein cofilin, which depolymerizes actin filaments that regulate actin reorganization. G-1 significantly increased phosphorylation of cofilin in the DH 5 and 15 minutes after infusion. Because phosphorylation inactivates cofilin, thereby increasing actin polymerization, these data suggest that activation of GPER may increase dendritic spine morphogenesis through actin polymerization. To verify the importance of actin polymerization in GPER-mediated dendritic spine morphogenesis and hippocampal memory enhancement, we applied an actin polymerization inhibitor, latrunculin A, which prevents de novo actin polymerization and promotes filament disassembly. We found that DH infusion of latrunculin A prevented G-1 from enhancing object recognition and spatial memory consolidation. These data suggest that hippocampal actin rearrangement plays an important role in GPER-mediated object and spatial memory enhancement. As a next step, we are currently determining the effects of latrunculin A on GPER-mediated hippocampal spine remodeling to confirm the importance of actin rearrangement in GPER-mediated dendritic spine morphogenesis. Collectively, these data support a critical role of actin polymerization in the GPER-induced regulation of hippocampal function in female mice.

Disclosures: J. Kim: None. **J.C. Schalk:** None. **W.A. Koss:** None. **K.M. Frick:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIMH grant RO1 MH107866

University of Wisconsin-Milwaukee Office of Undergraduate Research

Title: Dorsal hippocampal Wnt/β-catenin signaling is required for 17β-estradiol to enhance object memory consolidation in female mice

Authors: *L. TAXIER, M. M. KIEFER, S. M. PHILIPPI, A. M. FORTRESS, K. M. FRICK
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Abstract: The potent estrogen 17β-estradiol (E_2) enhances object recognition and spatial memory through activation of several cell signaling cascades in the dorsal hippocampus (DH), including ERK, PI3K, and mTOR. Previously, we demonstrated that object learning robustly activates the Wnt/β-catenin signaling pathway in the DH of male mice by rapidly increasing levels of β-catenin, phosphorylated GSK3β, and Cyclin D1 (Fortress et al., 2013, JNeurosci, 33:1219-1226). Moreover, we showed that activation of Wnt/β-catenin signaling in the DH is necessary for object recognition memory consolidation in males. Specifically, blockade of Wnt/β-catenin signaling via bilateral DH infusion of the Wnt/β-catenin antagonist Dickkopf-1 (Dkk-1) impaired object recognition memory consolidation in male mice. E_2 may modulate Wnt/β-catenin signaling through crosstalk with other pathways, such as PI3K signaling, that are similarly able to phosphorylate GSK3β and thus allow for downstream transcriptional activation. However, a role for Wnt/β-catenin signaling in the memory-enhancing effects of E_2 has yet to be elucidated. To determine whether Wnt/β-catenin signaling in the dorsal hippocampus (DH) is necessary for E_2-mediated memory enhancement, female C57/BL6 mice were ovariectomized and cannulated in the DH (bilateral) and dorsal third ventricle (unilateral). Immediately following training on object memory tasks, mice were infused with vehicle or Dkk-1 into the hippocampus, and vehicle or E_2 into the dorsal third ventricle. After either a 48 or 24 hour delay, memory consolidation was tested in object recognition or object placement tasks, respectively. The memory-enhancing effects of E_2 in both tasks were completely blocked by a non memory-impairing dose of Dkk-1, suggesting that activation of Wnt/β-catenin signaling in the DH is necessary for E_2 to enhance memory consolidation in ovariectomized females. Following completion of behavioral testing, mice were re-infused, and DH tissue collected at multiple time points for Western blotting and qPCR analysis. Western blotting and qPCR data indicate that E_2 activates, whereas Dkk-1 antagonizes Wnt/β-catenin signaling in the DH. In sum, these findings are the first step in a continuum of research that is expected to examine the ways in which E_2 interacts with Wnt/β-catenin signaling across the lifespan.

Disclosures: L. Taxier: None. **M.M. Kiefer:** None. **S.M. Philippi:** None. **A.M. Fortress:** None. **K.M. Frick:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

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Support: University of Wisconsin-Milwaukee College of Letters and Science

UWM Research Growth Initiative

R01DA038042

UWM Advanced Opportunity Program Fellowship

American Psychological Foundation/Council of Graduate Departments of Psychology Scholarship

Title: Chemogenetic investigation of dorsal hippocampal-medial prefrontal interactions in estradiol-mediated enhancement of object memory consolidation in female mice

Authors: *J. J. TUSCHER, L. R. TAXIER, K. M. FRICK
Psychology Dept., UW-Milwaukee, Milwaukee, WI

Abstract: Dendritic spine plasticity is thought to be essential for the formation and consolidation of memories. Both natural fluctuations and systemic administration of the sex-steroid hormone 17β-estradiol (E_2) can regulate spine density in the dorsal hippocampus (DH) of rodents. Recently, we found that infusion of E_2 directly into the DH increases dendritic spine density in the DH and medial prefrontal cortex (mPFC), and that these effects depend upon rapid activation of the extracellular signal-regulated kinase (ERK) and mammalian target of rapamycin (mTOR) cell-signaling pathways in the DH. These intriguing findings highlight a previously unexplored interaction between the DH and mPFC that may have important implications for understanding how E_2 regulates memory. As such, these data led us to question whether interactions between the DH and mPFC are necessary for the E_2-induced memory enhancements that we have previously observed in hippocampus-dependent object tasks (Fernandez et al., 2008; Fortress et al., 2013; Boulware et al., 2013). To investigate whether the DH and mPFC collaborate to facilitate object memory consolidation, we utilized inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to inactivate the mPFC immediately after object training and prior to DH infusion of E_2. Preliminary data suggest that DREADD-mediated inactivation of the mPFC prevents the memory-enhancing effects of DH-infused E_2 on object memory consolidation. Ongoing studies are evaluating the extent to which inactivation of the mPFC also prevents DH-infused E_2 from increasing spine density the DH and mPFC. Together,

these studies will provide critical insight into the estrogenic regulation of memory formation in female mice.

Disclosures: J.J. Tuscher: None. **L.R. Taxier:** None. **K.M. Frick:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: F.02. Behavioral Neuroendocrinology

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

Title: The rapid effects of hippocampally-synthesized estrogens on recognition learning in ovariectomized mice

Authors: *T. MARTIN[1], E. HARMAN[2], E. CHOLERIS[3]
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Abstract: The hippocampus has been implicated in various types of learning and memory, including social and object recognition. Estrogens can act on the brain via long-term genomic and/or very rapid mechanisms (Tuscher et al., 2016; Phan et al., 2015). Studies have demonstrated that infusion of exogenous estrogen into the hippocampus before and shortly after a learning event leads to enhanced recognition memory via rapid mechanisms. In addition, the hippocampus has been found to synthesize its own estrogens from testosterone via the enzyme aromatase. The role of locally-synthesized endogenous estrogens within this brain region, and their rapid enhancing effects on memory, have also been explored (Phan et al., 2015). A significant reduction of estrogen synthesis with an aromatase inhibitor shortly after learning led to impaired long-term object recognition memory (Tuscher et al., 2016). The role of hippocampally synthesized estrogens in the initial, short-term memory/learning of recognition tasks, however, is still unclear. Here we infused the aromatase inhibitor Letrozole at the three doses of 0.005, 0.025, and 0.5 µg/hemisphere or 2% dimethyl sulfoxide (DMSO) vehicle bilaterally into the dorsal hippocampus of 2-month old ovariectomized CD1 mice 15 minutes before being run on either a social or an object recognition paradigm, where two stimuli (either conspecifics or objects, respectively) were repeatedly introduced into the home cage of experimental mice for a total of 3 habituation periods (each lasting 4-minutes), followed by a test period (also 4-minutes), where a novel stimulus was presented in place of one of the repeated stimuli. The phases of the paradigms were separated by 3-minute rest periods where the stimuli were removed. Testing was completed within 40 minutes of treatment, targeting the rapid, non-

genomic effects of estrogens. We hypothesized that subjects treated with Letrozole would demonstrate impaired recognition learning. The results of this study will contribute to a greater understanding of what role physiological estrogens within the hippocampus play in recognition learning. These results may also help to refine the pharmalogical treatments used to treat post-menopausal women who experience cognitive deficits by allowing for the development of more precise drugs that target specific rapid pathways that estrogens act through.

Disclosures: T. Martin: None. **E. Harman:** None. **E. Choleris:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.08/NN30

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R01AG041374

Title: Repeated restraint stress decreases nuclear estrogen receptor alpha levels in the hippocampus of female rats

Authors: *N. E. BAUMGARTNER[1,2], J. M. DANIEL[1,2,3]
[1]Neurosci. Program, [2]Brain Inst., [3]Dept. of Psychology, Tulane Univ., New Orleans, LA

Abstract: Previous work in humans and animal models indicates that increased levels of brain estrogen receptor alpha (ERα) are beneficial for cognitive function, even in the absence of circulating estrogens. Additionally, our lab has shown in rats that previous midlife exposure to estradiol following ovariectomy exerts positive effects on hippocampal-dependent learning and memory and increases nuclear hippocampal ERα levels beyond the period of hormone exposure. This lasting increase in nuclear ERα levels in the hippocampus is at least partly due to decreased degradation of ERα, as indicated by decreased interaction between ERα and the ubiquitin ligase C-terminus of Hsc-70 interacting protein (CHIP). It is currently unknown if other manipulations that impact protein degradation also affect hippocampal ERα levels. Therefore, the current study examines whether stress, which also affects ubiquitination, would lower protein levels of nuclear ERα in the hippocampus of young adult female rats. Estradiol-treated ovariectomized rats underwent five days of two-hour long restraint stress or control treatment. Rats were killed immediately following the final restraint stress period and hippocampi were dissected and processed for subcellular fractionation. The nuclear compartment of hippocampal lysates was extracted using a commercially available kit and further processed for western blotting. Repeated restraint stress resulted in significantly decreased nuclear protein expression of hippocampal ERα in estradiol-treated ovariectomized young adult female rats. These results suggest that life events such as stress can impact ERα levels in the hippocampus.

Disclosures: **N.E. Baumgartner:** None. **J.M. Daniel:** None.

Poster

159. Hormones and Cognition: Estrogens

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R01 MH107886-01A1

University of Wisconsin-Milwaukee College of Letters and Science

Title: Effects of dorsal hippocampal estradiol treatment and aromatase inhibition on memory consolidation in male mice

Authors: *W. A. KOSS, R. L. GREMMINGER, S. M. PHILIPPI, K. M. FRICK
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: In ovariectomized females, 17β-estradiol (E_2) increases memory consolidation in the object placement (OP) and object recognition (OR) tasks. This enhancement depends on the rapid activation of cell-signaling cascades including the ERK pathway. However, the mechanisms through which E_2 may regulate memory consolidation in males is unknown. Here, ovariectomized female and both intact and castrated male mice were infused with vehicle or E_2 directly into the dorsal hippocampus (DH) immediately after training in object tasks. E_2 enhanced memory consolidation in all groups. To determine if the mechanisms underlying memory enhancements in males were similar to females, castrated males were infused with vehicle or the ERK phosphorylation inhibitor U0126 into the DH immediately before infusion of vehicle or E_2 into the dorsal third ventricle. Unlike in females, U0126 did not block the enhancement of memory by E_2. Accordingly, E_2 did not increase levels of phosphorylated ERK in the DH as has been demonstrated in females. However, E_2 did increase the transcription factor CREB in the dorsal hippocampus of both male and female. Together, these data indicate sex differences in the molecular mechanisms underlying E_2-induced memory enhancement. To continue investigating the role of E_2 in object and spatial memory, we examined putative sex differences in the effects of aromatase inhibition on memory. DH infusion of the aromatase inhibitor letrozole disrupts OR and OP memory consolidation in ovariectomized females. Preliminary results indicate that DH infusion of letrozole significantly impairs memory in castrated males but not intact males. These studies demonstrate that E_2 is critical for memory consolidation in both sexes but suggest sex differences in underlying molecular mechanisms. Additionally, preliminary data suggest that inhibiting hippocampal-synthesized E_2 in males impairs memory only in the absence of circulating androgens. The mechanisms underlying the

memory-enhancing properties of E_2 in males and the relationship between androgens and *de novo* hippocampal E_2 will be further explored.

Disclosures: W.A. Koss: None. **R.L. Gremminger:** None. **S.M. Philippi:** None. **K.M. Frick:** None.

Poster

159. Hormones and Cognition: Estrogens

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Topic: F.02. Behavioral Neuroendocrinology

Support: NSF IOS 13-18490

NIH P50AT006268-05

NIH P30 AG034464

Title: Estradiol regulation of energy substrates and memory modulation

Authors: *W. WANG, D. KOROL
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Abstract: Estrogens enhance learning and memory on hippocampus-sensitive tasks particularly when memory load is high. We have tested whether these cognitive effects reflect modulation by estradiol of metabolic substrates in this brain region. Ovariectomized rats received either estradiol benzoate (EB; 4.5 µg/kg) or oil vehicle (s.c.) 24 and 48 hours prior to microdialysis. Rats with EB treatment had significantly higher hippocampal extracellular glucose concentrations than did oil-treated rats. In contrast, EB did not significantly alter extracellular glucose concentrations in the striatum. To test the importance of glucose for effects of EB on spatial working memory, we infused glucose (25 nmol) or saline (0.5 µL across 2 min) into the hippocampus just prior to spontaneous alternation testing in rats treated with EB or oil treatments for two days. EB had no effect on alternation scores when rats were allowed to enter arms freely without imposed delay. However, when a 20-sec delay was imposed between arm entries, EB robustly enhanced alternation from chance levels in oil-treated controls. In the delayed alternation task, glucose enhanced working memory in the oil-treated rats, which otherwise had low alternation scores, but did not enhance alternation scores in EB-treated rats. The results show that glucose infusions enhance memory under the condition, ovariectomized oil-treated, in which rats have low extracellular glucose levels and have poor working memory. In contrast, glucose did not enhance memory in EB-treated rats in which extracellular glucose was high and memory scores were significantly above chance. Thus, EB regulation of the availability of metabolic substrates may contribute to estrogenic enhancement of hippocampus-sensitive cognitive

functions. We are currently measuring hippocampal extracellular glucose in response to working memory testing to determine whether EB potentiates or attenuates initial testing-related depletion and subsequent elevation in glucose. Together the findings support our past evidence using male rats suggesting that metabolic substrate availability in the hippocampus modulates learning and memory.

Disclosures: W. Wang: None. **D. Korol:** None.

Poster

159. Hormones and Cognition: Estrogens

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Topic: F.02. Behavioral Neuroendocrinology

Support: NSF IOS 13-18490

NIH P50AT006268-05

NIH P30AG034464

Title: Estradiol interacts with age-related changes in response and place learning in female F344 rats

Authors: *D. L. KOROL[1], W. WANG[1], C. G. WHITE[2], L. A. CASTELAN[2], P. E. GOLD[2]
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Abstract: During aging, male F344 rats exhibit shifts from hippocampus-sensitive place to striatum-sensitive response learning strategies. This experiment examined the effects of age and estrogen treatment on learning in female F344 rats. In young adult female Sprague-Dawley and Long-Evans rats, estradiol enhances place learning and impairs response learning. Given the loss of estrous cyclicity together with the loss of sensitivity to estrogens after ovariectomy, we hypothesized that the age-related shift in learning strategy would be even more robust in females than in males. To test this, young (3-mo-old) and old (25-mo-old) F344 rats were trained on response or place versions of a T-shaped maze three weeks following ovariectomy. Rats were treated with either oil vehicle or 45 µg/kg estradiol benzoate (EB) 48 and 24 hr prior to training. On the response task, old oil-treated F344 rats had impaired learning as compared to young rats, directly opposite the effects of age in male F344 rats where old rats outperform young rats. EB treatment in both young and old female rats impaired responses learning relative to their age-matched oil controls, suggesting that the striatum retains its sensitivity to estradiol with age. In the place task, learning rates were not different between young and old oil-treated rats, also a result quite different from that seen in male rats where young rats outperform old rats. Moreover, EB enhanced place learning in old but not young rats, suggesting that the hippocampus of old

female F344 rats retains its sensitivity to estradiol, a conclusion different from our predictions. Perhaps the progesterone depletion resulting from ovariectomy restored hippocampus-sensitive place learning or the 3-week interval of estradiol depletion after ovariectomy was not sufficiently long to produce declines in estrogen receptors, possibilities proposed by others. Overall, the findings showed that, unlike males, aged ovariectomized females retained their ability to solve place tasks but decreased their ability to solve response tasks. In addition, estradiol effectively modulated place and response learning in old female rats, suggesting that with age, both hippocampus and striatum remain sensitive to estrogens after relatively short periods of peripheral hormone depletion.

Disclosures: D.L. Korol: None. **W. Wang:** None. **C.G. White:** None. **L.A. Castelan:** None. **P.E. Gold:** None.

Poster

159. Hormones and Cognition: Estrogens

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Program#/Poster#: 159.12/OO1

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH grant 5P50AT006268

Title: The effects of components of licorice root on a novel object task in rats

Authors: *P. KUNDU[1], D. L. KOROL[2], W. G. HELFERICH[1], C. E. ONDERA[1], S. L. SCHANTZ[1]
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Abstract: It is well established that estrogens modulate cognition in a task-dependent manner. Many dietary supplements contain estrogenic compounds, the efficacy and safety of which are poorly understood. This study investigated the efficacy of components of licorice root (*Glycyrrhiza glabra)* to alter performance on a striatum-sensitive double object recognition (DOR) task. We investigated whole licorice root power (LRP), a methanol extract of licorice root (LRE), and isoliquiritigenin (ISL), a pure compound with estrogenic activity that is found in licorice root. Young adult (3-month old) Long-Evans female rats were ovariectomized (OVX) and exposed to LRP, LRE or ISL at a concentration of 5%, 0.5% or 0.075% respectively of the diet for three weeks prior to testing. Estradiol has been shown to impair performance on the DOR task and thus was included as a negative control. Rats in the estradiol group were injected subcutaneously 48 and 24 hours prior to testing with 45 µg/kg of estradiol. In the DOR task, rats were allowed to explore two objects in a black Plexiglas® chamber while object exploration time was recorded. Following three 5-min trials (separated by 3-min intertrial intervals) during which

rats decrease object exploration, a fourth 5-min test trial was introduced in which the objects were replaced with two new objects and exploration time was again recorded. An increase in object exploration time in the test trial suggests that the rat detected the change in objects. As expected, estradiol impaired performance on the DOR task, however ISL, LRP and LRE exposure failed to change DOR. This is contrary to the actions of most other estrogens tested to date, which tend to impair performance on striatum-sensitive tasks in young-adult OVX rats. Our previous work shows that ISL and LRE improve performance on a hippocampus-sensitive metric change in object location task in OVX rats. Together, these findings suggest that components of licorice root may have the beneficial effects of estrogens on cognition without the risks.

Disclosures: **P. Kundu:** None. **D.L. Korol:** None. **W.G. Helferich:** None. **C.E. Ondera:** None. **S.L. Schantz:** None.

Poster

159. Hormones and Cognition: Estrogens

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.13/OO2

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC

Title: Social recognition is mediated by the interaction between the rapid effects of estrogens and oxytocin

Authors: *P. PALETTA[1], S. HOWARD[1], K. ALI[1], E. CHOLERIS[2]
[2]Psychology, [1]Univ. of Guelph, Guelph, ON, Canada

Abstract: In a social species, like humans and mice, being able to recognize an individual that has been encountered before is an important ability. This ability is known as social recognition, and allows for the development of several functions including social bonds with others like mates and offspring, as well as being able to recognize those that could pose a threat. Both estrogens and oxytocin (OT) have been implicated in mediating social recognition. Knockout studies have shown that when estrogen receptor alpha (ERα), oxytocin (OT), or the oxytocin receptor (OTR) are knocked out, social recognition is blocked suggesting that both estrogens and oxytocin are needed for proper social recognition functioning. It has been proposed that since both are required, there is likely an interaction between them. This would occur by estrogens binding to estrogen receptor beta (ERβ) and/or the G-protein coupled estrogen receptor (GPER) in the paraventricular nucleus (PVN) of the hypothalamus, one of the regions responsible for most of the OT production in the brain. ERβ and GPER colocalize with OT producing cells in the PVN, so estrogens binding to these receptors would facilitate the production and release of OT from this region. The OT will then bind with the OTR in the medial amygdala, which is

mediated by ERα, ERβ, and GPER, and facilitate social recognition. In order to test this, we first needed to determine whether 17β-estradiol (E2) infused into the PVN can facilitate social recognition in ovariectomized, CD-1 mice. My current results have shown that E2 in the PVN can rapidly facilitate social recognition at 25 and 50nM. Next, to determine if this occurs through an interaction with OT, an OTR antagonist will be infused into the medial amygdala while E2 is infused into the PVN. The mice will be run through a social recognition paradigm that is designed to be difficult, so that enhancing effects of treatments can be tested. In this paradigm, two ovariectomized stimulus mice are presented in two habituation phases. Then in the test phase, one of the stimulus mice used in the habituation phases and a novel stimulus mouse are presented. If the novel mouse is investigated more, it would suggest that the other mouse is familiar to them and that social recognition occurred. The first habituation phase began 15 minutes after the infusion of E2 into the PVN and the OTR antagonist into the medial amygdala. In addition, this paradigm takes place within 40 minutes to test the rapid effects of estrogens. If the antagonist blocks the facilitative effect that E2 in the PVN has on social recognition, it would show support for the idea that estrogens and OT interact to facilitate social recognition. Funded by NSERC.

Disclosures: P. Paletta: None. **S. Howard:** None. **K. Ali:** None. **E. Choleris:** None.

Poster

159. Hormones and Cognition: Estrogens

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH41256

Hope for Depression Research Foundation

Title: Estradiol add-back in BDNF Val66Met mice mimics the behavioral and transcriptional phenotype of premenstrual dysphoric disorder

Authors: *J. MARROCCO[1], G. H. PETTY[1], N. DUBEY[2], J. F. HOFFMANN[3], K. F. BERMAN[4], D. GOLDMAN[6], P. J. SCHMIDT[5], B. S. MCEWEN[1]
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Abstract: Premenstrual dysphoric disorder (PMDD), a severe form of premenstrual syndrome, affects over 5% of women, with symptoms similar to generalized anxiety disorder and major

depression. Clinical data indicates that women suffering from PMDD are differentially sensitive to circulating ovarian hormones compared to healthy women. Altered brain-derived neurotrophic factor (BDNF) levels in the limbic system, such as the hippocampus, are correlated with depression and anxiety in both humans and rodent models. The BDNF Val66Met single-nucleotide polymorphism is a common human variant of the gene, with Met carriers displaying altered sensitivity to stress and ovarian hormones. We hypothesized that 17β estradiol (E) add-back treatment could modulate behavior and RNA transcription in Met carriers in a way that recapitulates menstrual cycle-related behavioral sensitivity reminiscent of PMDD. To this end, we ovariectomized a knock-in mouse heterozygous for the Met allele of the BDNF gene ($BDNF^{+/Met}$) and their matched wild type ($BDNF^{+/+}$). After a 10 day-recovery period, mice were treated with either estradiol (200nM E/0.1% ethanol) or vehicle (0.1% ethanol), administered via drinking water for six weeks. A battery of behavioral tests was performed during treatment. In the open field test, E treatment induced an anxiogenic effect on $BDNF^{+/Met}$ mice, and in the splash test E treatment induced depressive-like behavior in $BDNF^{+/Met}$ mice, but not in $BDNF^{+/+}$. This indicates that Met carriers display a heightened emotional sensitivity to E treatment. Thus, the behavioral phenotype of Met carriers resembled that of women suffering from PMDD, who experience increased depressive symptoms after E add-back treatment. The behavioral similarities between $BDNF^{+/Met}$ mice and women with PMDD prompted us to perform a comparative whole-genome RNA-sequencing analysis between mouse ventral hippocampus and lymphoblastoid cell cultures from healthy women and women suffering from PMDD. RNA sequencing revealed a greater overlap in E-induced gene expression between $BDNF^{+/Met}$ mice and women with PMDD than between $BDNF^{+/+}$ mice and healthy women. Interestingly, this overlap included several genes belonging to the ESC/E(Z) complex, such as *SIRT1*, *PHF19* and *MTF2*. Together, our data indicate that $BDNF^{+/Met}$ mice recapitulate PMDD both behaviorally and transcriptionally, suggesting the Met allele as a risk factor for PMDD.

Disclosures: **J. Marrocco:** None. **G.H. Petty:** None. **N. Dubey:** None. **J.F. Hoffmann:** None. **K.F. Berman:** None. **D. Goldman:** None. **P.J. Schmidt:** None. **B.S. McEwen:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.15/OO4

Topic: F.02. Behavioral Neuroendocrinology

Support: CNPQ

FAPESP

CAPES/PROEX

Title: Effects of estrogen therapy on especific brain regions in animal model of perimenopause induced by diepoxide 4-vinylcyclohexene (VCD)

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Abstract: Perimenopause is related with intense neuroendocrine, metabolic and behavioral changes. The diepoxide 4-vinylcyclohexene (VCD) treatment is a well-established experimental model for perimenopause studies, due to VCD ability to accelerate the natural process of follicular atresia. Although estrogen levels are normal or even high during perimenopause, estrogen therapy can be beneficial for symptomatic perimenopausal women. The aim of this study was to investigate whether gradual follicular depletion induced by VCD results in changes in the neurochemistry of female rats in brain nuclei that control mood and the role of estradiol. Female rats (28 days) were daily injected with VCD or corn oil (O) for 15 days. Around 55 days after the first injection, pellets of 17β-estradiol (E) or O were inserted s.c (Groups O+O; VCD+O; VCD+E). Around 21 days after, rats O+O and VCD+O were decapitated in the morning of diestrus while rats VCD+E were decapitated exactly 21 days after the onset of E therapy, between 0900 h and 1100 h. Brains were removed and the hippocampus and amygdala punched out for the analysis of estrogen receptor β (ERβ) and progesterone receptor (PR) mRNA levels by PCR/RT. Another set of rats under the same experimental design was perfused for TPH immunohistochemistry in Dorsal Raphe Nuclei (DRN). In hippocampus, PR gene expression did not differ between groups, but ERβ expression was higher in VCD+E group. While in amygdala no significant differences were observed in expression of both genes evaluated in any of the groups, the number of TPH cells in DRN was decreased in the VCD+O group, and estradiol was able to reverse this effect, acting mainly in the caudal region. In conclusion, the ability to up-regulate ERβ expression seems to be the estradiol key function to rectify the impairments in the serotonergic system induced by ovarian failure. Futures studies are needed to evaluate the use of ERβ agonists for the treatment of mood disorders during perimenopause as an alternative to the use of estradiol.

Disclosures: **N. Pestana:** None. **J.A. Anselmo-Franci:** None. **B. Kalil:** None. **J.A. Rogrigues:** None. **L.L.K. Elias:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

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Topic: F.02. Behavioral Neuroendocrinology

Support: National Postdoctoral Fellow (NPDF/2016/000060) award from Department of Science and Technology, Government of India

Senior Research Fellowship award (45/13/2011-BMS/Immunology) award from Indian Council of Medical Research, Government of India

Title: Estrogen deficiency and neurodegeneration: An inflammatory tale

Authors: *P. KUMAR[1], P. DHAR[2]
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Abstract: Ever since the first demonstration of estrogen concentrating cells in the brain by Donald Pfaff in early 1960s, the role of this female sex hormone has been under immense scrutiny in different areas of brain. The two most widely acclaimed non-reproductive functions of estrogen have been associated with i) memory and cognition and ii) neuroprotection. In females, postmenopausal aging and decreased estrogen levels go hand in hand thereby predisposing them to a multitude of age related pathophysiological events including the cognitive decline and Alzheimer's disease. There is decent amount of evidence suggesting the association between estrogen (E2, 17β estradiol) and hippocampal and cerebellar activity. Localization of estrogen receptors (ERs) in the brain areas related to learning and memory provides the evidence of these areas being the target zones for the hormone activity. Identification of ERs in other brain areas further expands thepleotropic nature of this hormone. In our current study, there has been an attempt toexplore the role of estrogen in crosstalk between the nervous, endocrine and immune features in hippocampus of female rats.

Immunohistochemistry, Western blot, qRT-PCR and ELISA techniques were used for proteomic and genomic analysis. The observations revealed decreased synaptic activity, degenerative cytoarchitectural changes, microglial activation, altered levels of ERs, anti-apoptotic proteins and concomitant changes in the expression of complement proteins (C1q, C3 and C3aR) and pro- and anti-inflammatory cytokines (IL-6, TNF-α and IL-10) inhippocampus of Ovariectomized (OVX) rat model. Long-term estrogen therapy to OVX rats could maintain synaptic plasticity (synaptophysin) and regulate microglial activity, apoptotic molecules (Bax and Bcl2), complement proteins and pro-inflammatory cytokines.

These observations add a new perspective to the neuroprotective and neuromodulatory effects of estrogen based on its role in complement system and pro-inflammatory cytokines on one hand and modulation of apoptosis associated proteins on the other.

(National Postdoctoral Fellow award (PDF/2016/000060) from Department of Science and Technology, Government of India and The Senior Research Fellowship award (45/13/2011-BMS/Immunology) from Indian Council of Medical Research (ICMR)to P. Kumar is duly acknowledged.)

Disclosures: P. Kumar: None. **P. Dhar:** None.

Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.17/OO6

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: A dose that is just right? Drospirenone dose-dependently affects cognitive outcomes

Authors: *S. V. KOEBELE[1,2], M. L. POISSON[1,2], J. M. PALMER[1,2], C. BERNS-LEONE[1,2], S. PATEL[1,2], I. M. STROUSE[1,2], H. A. BIMONTE-NELSON[1,2]
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Abstract: Drospirenone is a fourth generation progestin, or synthetic analog of natural progesterone, and is the progestin component of several popular oral contraceptives (e.g. Yaz®) as well as hormone therapies for menopausal women (e.g. Angeliq®) (Archer et al., 2015; Hoffman et al., 2012). Basic science research has shown that progestogens have significant impacts on the body and brain that extend beyond their role in reproductive endocrinology, including effects on cognition. These effects are dependent upon the type of progestin administered, dose, and duration of treatment. Our laboratory has previously shown that chronic treatment with clinically-used progestogens, including medroxyprogesterone acetate and norethindrone acetate, resulted in spatial memory impairments, and natural progesterone reversed the beneficial effects of estrogen administration on cognition (Bimonte-Nelson et al., 2004, 2006; Braden et al., 2010, 2011, 2015, 2017). Unlike other synthetic progestins, drospirenone is most similar in its pharmacological profile to progesterone, and, notably, has anti-androgenic and anti-mineralocorticoid properties without concomitant glucocorticoid activity (Schindler et al., 2003), making this a unique progestin of interest to investigate for its effects on cognition, including spatial memory and anxiety-like behaviors. Here, young adult Fischer-344-CDF female rats were ovariectomized and subsequently administered one of three doses of drospirenone or vehicle treatment. To evaluate the impact of drospirenone on spatial working and reference memory, a battery of behavior tasks, including the water radial-arm maze and Morris water maze, was utilized; anxiety-like behavior was evaluated using the open field task. Preliminary results indicate that a daily, subcutaneous injection of a medium dose of drospirenone enhanced spatial memory when the working memory load was taxed compared to control subjects. There was also a trend toward a dose response to drospirenone treatment in the open field task, such that animals that received the medium dose of drospirenone tended to

exhibit anxiolytic behavior compared to controls. Given that drospirenone appears to have unique and beneficial effects on cognition that are different from other clinically-available progestins, further investigation into these observed drospirenone-induced cognitive enhancements are currently underway.

Disclosures: S.V. Koebele: None. **M.L. Poisson:** None. **J.M. Palmer:** None. **C. Berns-Leone:** None. **S. Patel:** None. **I.M. Strouse:** None. **H.A. Bimonte-Nelson:** None.

Poster

159. Hormones and Cognition: Estrogens

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Program#/Poster#: 159.18/OO7

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: Together, but not for better? Evaluating the cognitive effects of ethinyl estradiol and drospirenone given individually and in combination in young OVX rats

Authors: *V. L. PENA[1,2], M. L. POISSON[1,2], S. V. KOEBELE[1,2], C. CROFT[1,2], S. PATEL[1,2], I. M. STROUSE[1,2], H. A. BIMONTE-NELSON[1,2]
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Abstract: Among women ages 15-44 who use some form of contraception, approximately 28% of users take oral contraceptives, of which combined oral contraceptives (COCs) are most prevalent (Mosher & Jones, 2010). COCs are comprised of an estrogen and progestogen component. For the past decade, a popular COC formulation has been composed of ethinyl estradiol (EE) and drospirenone (DRSP). EE has been shown to result in dose-dependent spatial working memory impairments and decrease ChAT-positive cells in the basal forebrain, which correlated with poorer working memory performance (Mennenga et al., 2015). We have shown that some clinically-used synthetic progestins, such as medroxyprogesterone acetate and norethindrone acetate, impair rat cognition (Braden et al., 2010, 2011, 2017). Progesterone administration can attenuate the beneficial cognitive effects and growth factor increases due to exogenous 17β-estradiol (E2) treatment in preclinical models (Bimonte-Nelson et al., 2004, 2006). DRSP is a fourth generation progestogen that is more closely related to endogenous progesterone compared to other synthetic progestins. DRSP has anti-androgenic and anti-mineralocorticoid effects without glucocorticoid activity, thus potentially resulting in differential cognitive effects compared to other synthetic progestins. It is currently unknown whether EE and

DRSP interact to produce unique effects on cognition than either one alone. Given that most women take COCs for an extended time period, it is important to model this preclinically and investigate how combined EE and DRSP impact cognitive performance when given chronically. Young Fischer-344-CDF rats were ovariectomized (Ovx). Rats received daily injections of vehicle, DRSP, EE, or a combination of EE plus DRSP. They were tested on a battery of behavioral tasks: the water radial-arm maze (WRAM; spatial working and reference memory), Morris maze (spatial reference memory), and open field task (anxiety like and locomotor behavior). Results suggest that DRSP treatment alone enhanced WRAM acquisition compared to vehicle treatment (a replication of our prior work; unpub observations). Further, low dose EE plus DRSP impaired spatial working memory on the WRAM compared to low dose EE alone. Prior work from our and other laboratories indicates that progesterone attenuates E2-related cognitive benefits; the current results extend these findings regarding endogenous ovarian hormones to include clinically-relevant synthetic hormones commonly used in COCs. Further investigation into the differential cognitive effects of independent and combined estrogen and progestogen administrations are currently underway.

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Poster

159. Hormones and Cognition: Estrogens

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Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer’s Disease Core

Title: Memory impairments from 17beta-estradiol plus levonorgestrel hormone therapy are dependent on their ratio

Authors: *A. V. PRAKAPENKA[1,2,3,5,6], C. BERNS-LEONE[2,5], V. L. PEÑA[2,5], S. NORTHUP-SMITH[2,5], R. MELIKIAN[2,5], S. PATEL[2,5], D. S. LADWIG[2,5], R. HIROI[2,5], A. L. MANN[2,5,7,8], M. J. VALENZUELA SANCHEZ[2,5,7,8], R. W. SIRIANNI[6,4], H. A. BIMONTE-NELSON[2,5]
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[8]Psychology at ASU High Sch. Program, RISE (Research Intensive Scientific Experience), Tempe, AZ

Abstract: 17β-estradiol (E2) and Levonorgestrel (Levo) are two hormones clinically used in hormone therapy to alleviate symptoms associated with menopause. Our and other laboratories have previously shown that E2 alone and Levo alone can have beneficial effects on cognition in a rodent model of surgical menopause. However, since E2 and Levo are typically given in the clinic together (e.g., ClimaraPro), it is vital to understand how different E2 to Levo combination ratios impact cognitive performance following a decrease in circulating ovarian hormone levels. Thus, two studies were conducted with the overarching aim of examining the cognitive effects of E2 plus Levo hormone combination treatments using a rat model of surgical menopause. In both studies, middle-aged female rats were ovariectomized and randomly assigned to receive daily subcutaneous injections of either vehicle or hormone treatment. To evaluate cognitive performance, the water-radial arm maze (WRAM) was used to assess spatial working and reference memory and the Morris water maze was used to assess spatial reference memory. The goal of the first study was to determine how E2 treatment dose impacted cognitive performance. Findings from this study revealed that the low E2 dose enhanced working memory performance compared to both vehicle control and high E2 dose treatments. Consequently, the low E2 dose was used in combination with varying doses of Levo in the second study; this allowed us to examine the cognitive effects of 5:1, 3:1, and 1:2 E2 to Levo combination ratios. We found that the addition of a high dose of Levo to E2 (a 1:2 E2 to Levo ratio) impaired spatial memory performance on the WRAM. The hormone ratio found in ClimaraPro, 3:1 E2 to Levo, also tended to impair spatial memory performance. Indeed, there was a linear dose response effect indicating that spatial working and spatial reference memory performance was incrementally impaired as Levo dose increased when combined with E2. Western blot analyses on brain regions involved in cognitive function are currently being completed to elucidate neuromechanisms mediating the cognitive effects seen with the hormone treatments tested in these two studies. Together, the behavioral results suggest that the E2 plus Levo combination is likely not neutral for cognitive function, even though each hormone on its own has been previously shown to be cognitively beneficial, in a model of surgical menopause. Moreover, cognitive impairment tended to increase with the addition of increasing Levo dose to a cognitively beneficial E2 dose, indicating that the ratio of estrogen (E2) to progestin (Levo) hormone combination is a critical contributing factor to cognitive outcomes.

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Poster

159. Hormones and Cognition: Estrogens

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 159.20/OO9

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant R15-HD085102-01

Title: Simvastatin increases neuroestradiol in female zebra finches

Authors: *C. R. MCDERMOTT[1], N. NARAYANAN[2], S. SRINIVASAN[2], M. L. PHAN[2], D. S. VICARIO[2], C. L. PYTTE[1]
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Abstract: Cholesterol is vital to normal brain function, including learning and memory. Brain cholesterol is produced de novo as the blood brain barrier (BBB) prevents the uptake of cholesterol from the periphery. Statins are a family of drugs that are highly effective in decreasing plasma cholesterol to combat cardiovascular diseases. However, statins can also cross the BBB and decrease levels of neurocholesterol, perhaps related to reports of memory impairment corresponding to statin use. Statins are also approved for use in pediatric populations, thus we are particularly interested in potential neural effects of statin use in juveniles. We hypothesized that statin-related memory impairment may arise from disruption of neuroestradiol (E2), which is synthesized from cholesterol and functions in memory formation. We tested this idea in the caudomedial nidopallium (NCM) of the zebra finch, a higher order auditory association area which functions in the formation and storage of auditory memories for conspecific songs and is enriched in aromatase and E2. We administered daily oral doses of 40 mg/kg of simvastatin in water, or an equal volume of water vehicle, to juvenile male and female zebra finches beginning at ages 32-57 days post hatch and sacrificed birds 122-415 days after onset of statin administration. Zebra finches are considered adults at ~90 days. We isolated neurostereoids independently in left and right NCM followed by enzyme-linked immunosorbent assays (ELISAs) to detect concentrations of E2 in this brain area. All data were obtained blind to treatment and analyzed using a 2 factor ANOVA (sex X treatment with hemisphere as a repeated measure). In females, we found that statins increased levels of E2 bilaterally, while preliminary data in males suggest that statins did not alter E2 levels. Additionally, both control and statin-treated females had higher levels of E2 than males. Interestingly, sex differences in statin efficacy have been observed in clinical studies reporting that females are less likely to achieve their lipid goals than males and suffer from greater side effects. Although it is unclear why simvastatin treatment resulted in an increase (rather than the hypothesized decrease) in brain levels of E2 in females, these finding suggest a sex difference in central effects of statins, which may contribute to sex differences observed in cognitive deficits.

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Poster

160. HPG Axis

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 160.01/OO10

Topic: F.03. Neuroendocrine Processes

Support: NIHR21-HD83389

Title: Estradiol regulates effects of short-term food deprivation on the gonadotropin-releasing hormone (GnRH) - pituitary luteinizing hormone (LH) Axis

Authors: *M. SHAKYA, K. P. BRISKI
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Abstract: Reproduction is subject to strict regulation by metabolic status. Estrous cycle patterns of estradiol (E) secretion impact bodily metabolic balance as food intake declines and energy state becomes (paradoxically) more negative as E levels rise. Short-span interruption of fuel consumption, planned or unplanned, has physiological relevance to modern life. This project used a characterized E replacement paradigm that re-establishes plasma hormone levels at estrous cycle peak (EP) versus nadir (EN) concentrations to address the hypothesis that physiologically-distinct patterns of E secretion uniquely modulate GnRH-LH reactivity to short-term food deprivation (FD) of increasing, e.g. 12- (FD-12) or 18- (FD-18) hour duration. Hindbrain signals of metabolic imbalance inhibit the reproductive neuroendocrine axis; here, groups of FD animals were injected into the caudal fourth ventricle with the AMPK inhibitor Compound C (Cc) or vehicle to investigate whether dose-dependent E actions involve this energy sensor. Results show that E determines directionality of hindbrain AMPK-driven forebrain norepinephrine (NE) activity as FD-18 reduced or augmented rostral preoptic (rPO) NE accumulation FD in EN vs EP. Western blotting of rPO tissue from EN rats showed that GnRH-1 protein was resistant to FD-12 and -18 and insensitive to Cc. Yet, EP-FD-18 animals showed Cc-reversible reductions in rPO GnRH-1 and neuronal nitric oxide synthase protein profiles. FD did not modify rPO glutamate decarboxylase or anteroventral-periventricular nucleus prepro-kisspeptin expression, but both profiles were decreased by Cc in EP-FD-18. Arcuate hypothalamic nucleus (ARH) prepro-kisspeptin levels were diminished (EN) or elevated (EP) by FD-18, responses that were correspondingly unaltered or attenuated by Cc. Circulating LH was decreased in EP-FD-18. Data show that exposure to maximal cyclic E output sensitizes the GnRH-LH axis to FD inhibition by hindbrain AMPK-dependent mechanisms. Further research is warranted to determine if rPO nitrergic and/or ARH kisspeptinergic neurons mediate sensor control of the GnRH /LH axis during FD.

Disclosures: **M. Shakya:** None. **K.P. Briski:** None.

Poster

160. HPG Axis

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 160.02/OO11

Topic: F.03. Neuroendocrine Processes

Support: USDA 2013-00896

Title: Examination of age-related changes in NK3R expression and colocalization of KOR with GnRH neurons in the hypothalamus of female sheep

Authors: *M. BEDENBAUGH[1], C. A. RAINEY[2], R. B. MCCOSH[3], J. A. LOPEZ[3], R. L. GOODMAN[3], S. M. HILEMAN[3]
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Abstract: Increased gonadotropin-releasing hormone (GnRH) secretion is critical for puberty onset, but the neural mechanisms that underlie this increase are not well understood. Neurokinin B (NKB) and dynorphin may play a role in regulating GnRH secretion during pubertal development, as senktide, an NKB receptor (NK3R) agonist, and nor-BNI, a kappa-opioid receptor (KOR) antagonist, stimulate luteinizing hormone (LH) secretion in prepubertal ewes. However, where these effects occur is unknown. We first examined whether senktide or nor-BNI would increase LH secretion when placed in the preoptic area (POA). Ovary-intact prepubertal female sheep (n=7) received microimplants that were either empty, contained senktide, or contained nor-BNI. Each ewe received all three treatments on different days in a random order. Blood samples were collected every 12 min for 36 min before and 4 h after insertion of microimplants. Of the 7 ewes, 4 responded to senktide treatment. However, overall senktide treatment did not significantly increase mean LH concentration or LH pulse frequency. Two of the 7 ewes responded to nor-BNI treatment, but similar to senktide, nor-BNI did not significantly increase mean LH concentrations or LH pulse frequency when compared to empty microimplants. Because our previous work showed a robust LH response to senktide when placed in the POA of adult ewes, we next tested whether changes in POA expression of NK3R occur as ewes transition from a prepubertal to an adult state. Prepubertal ewes (n=4) or adult non-breeding season ewes (n=3) were ovariectomized (OVX) and tissue was collected two weeks later. NK3R expression was assessed by immunohistochemistry in four comparable sections in each the POA, paraventricular nucleus (PVN), retrochiasmatic area (RCh), and caudal arcuate nucleus (ARC) of each ewe. A greater number ($p < 0.02$) of NK3R-positive cells were found in the POA of adult ewes (48.6±1.7) when compared to prepubertal ewes (24.4±5.8). No

differences in NK3R-positive cell numbers were observed between the two groups in the PVN, RCh, or ARC. In addition, we also examined whether age affected the colocalization of KOR with GnRH neurons. Our preliminary examination of colocalization of GnRH and KOR in 2 prepubertal OVX ewes and 2 postpubertal OVX ewes shows that a high percentage (76%) of GnRH neurons contain KOR, but there do not seem to be large age-related changes in the degree of colocalization. In conclusion, changes in the NKB/NK3R system, specifically within the POA, may play a role in the pubertal increase in LH secretion, but evidence for large changes in KOR expression in GnRH neurons is lacking.

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Poster

160. HPG Axis

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 160.03/OO12

Topic: F.03. Neuroendocrine Processes

Support: PIP 110/14

Title: Hypothalamic GnRH release is stimulated by the combined action of melatonin and estradiol in the South American plains vizcacha (Lagostomus maximus)

Authors: *S. E. CHARIF[1], P. I. F. INSERRA[1], A. R. SCHMIDT[1], S. A. CORTASA[1], S. PROIETTO[1], M. C. CORSO[1], N. P. DI GIORGIO[2], V. LUX-LANTOS[2], A. D. VITULLO[1], J. HALPERIN[1], V. B. DORFMAN[1]
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Abstract: Melatonin (Mel) is secreted during the night and modulates hypothalamic-hypophyseal-gonadal (HHG) axis in order to coordinate environmental conditions with breeding. The South American plains vizcacha (*Lagostomus maximus*) is a rodent that displays massive polyovulation and HHG axis activity during pregnancy that leads to pseudo-ovulation at mid-gestation. We studied the effects of light availability, Mel alone or combined with estradiol (E_2), on vizcacha's HHG axis activity. Non-pregnant non-ovulating females (NPNO) and non-pregnant ovulating females (NPO) were exposed to continuous light (Light), continuous darkness (Dark), or 12:12 light-dark cycle (CTL) for 15 days. In a second approach, the effects of Mel and E_2 on GnRH secretion were analyzed. Hypothalamic GnRH content, serum LH, E_2, progesterone (P_4) and Mel levels were measured by RIA or ELISA, and hypothalamic expression of estrogen receptor α (REα) and β (REβ) was assessed by Western blot. Values were expressed as mean ± standard error. ANOVA was performed followed by Newman-Keuls Multiple Comparison test to

determine significant differences among groups ($p < 0.05$). GnRH, LH, E_2, and Mel levels of Dark NPNO animals were significantly higher than CTL and Light NPNO, whereas P_4 levels were significantly increased in Light NPNO vs. CTL and Dark NPNO. REα protein expression was significantly higher in Light NPNO animals vs. CTL and Dark NPNO, while REβ expression was significantly increased in Dark vs. CTL and Light NPNO groups. Dark NPO showed significantly higher levels of E_2 than CTL and Light NPO, whereas significant increase of Mel and LH were observed in Light NPO vs. CTL and Dark. GnRH content and P_4 levels remained unchanged between the three NPO groups. A significant increase of REα and decrease in REβ expression was detected in Light NPO vs. CTL and Dark NPO. The study of GnRH pulsatility showed that a significant increase in GnRH total secreted mass and mean pulse height was induced by Mel vs. CTL or E_2. In addition, Mel + E_2 significantly increased GnRH mass and decreased pulse number vs. the other groups. On the other hand, Mel + REβ agonist significantly increased GnRH total mass secretion vs Mel, Mel + E_2 and Mel + REα agonist groups. These results indicate that photoperiod is a key modulator of vizcacha's HHG axis activity but its effects depend on ovulation stage. In contrast to mice and rats, Mel induces GnRH release in the vizcacha. Strikingly, E_2 combined with Mel stimulates GnRH secretion, mainly through REβ. The action of Mel and E_2 feedback on the coordination of HHG axis activity with the environmental photic information may be essential to ensure the success of vizcacha´s reproduction.

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Poster

160. HPG Axis

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Program#/Poster#: 160.04/OO13

Topic: F.03. Neuroendocrine Processes

Support: JSPS Grant 17K15157 (CU)

JSPS Grant 26221104 (YO)

Title: Synaptically induced high frequency firing of the terminal nerve gonadotropin-releasing hormone 3 neurons and their release activity

Authors: *C. UMATANI, Y. OKA
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Abstract: The terminal nerve gonadotropin releasing hormone 3 (TN-GnRH3) neurons, one of the extrahypothalamic peptidergic neurons, have been intensively studied as a vertebrate model for the study of peptidergic neuromodulators. They are known to express GnRH3 peptides and project widely, especially densely to the brain regions related to behaviors and sensory processing. For example, they have been suggested to have neuromodulatory effects on the synaptic transmission in the optic tectum (Umatani et al., 2015) and in the olfactory bulb (Kawai, Oka, and Eisthen, 2009). They have also been suggested to be involved in the regulation of behavioral motivation in adult teleosts (Yamamoto et al., 1997). However, the release of neuropeptides from the TN-GnRH3 neurons and its mechanisms has not been studied in detail. A small number of previous studies have shown that peptidergic neurons, such as GnRH and kisspeptin neurons, generally have to fire at high frequency to release neuropeptides (Campos and Herbison 2014; Han et al. 2015). To study the regulatory mechanisms of neuropeptide release from TN-GnRH3 neurons, we analyzed the spontaneous and induced firing activities of TN-GnRH3 neurons by electrophysiology and possible neuropeptide release by Ca^{2+} imaging using *gnrh3*:*egfp* transgenic medaka. Electrophysiological experiments showed that local puffer application of glutamate, which mimics synaptic activation of TN-GnRH3 neurons, increases the frequency of firing activities. In addition, we newly found that TN-GnRH3 neurons show various patterns (regular low and high frequency, and bursting) of spontaneous firing activities depending on the stage of development. The spontaneous high-frequency firing, which was evident in juvenile fish, was suggested to be induced by glutamatergic inputs from the other neurons. Then, we analyzed their possible release activities by Ca^{2+} imaging of GFP-labeled TN-GnRH3 neurons by bulk loading of Fura2. Puffer application of glutamate to the TN-GnRH3 neurons caused their immediate and transient increase in $[Ca^{2+}]_{in}$ that is considered to be large enough to trigger neuropeptide release. This increase in $[Ca^{2+}]_{in}$ by glutamate showed a dose-response. Therefore, glutamatergic synaptic inputs are suggested to induce high frequency firing of TN-GnRH3 neurons, which is capable of inducing neuropeptide release. Such neuropeptide release from TN-GnRH3 neurons following their high frequency firing is suggested to play a key role in modulating neuronal processing in various brain regions in a coordinated manner.

Disclosures: C. Umatani: None. **Y. Oka:** None.

Poster

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Topic: F.03. Neuroendocrine Processes

Support: NIH ZIA NS002824-25

Title: Orphanin FQ inhibits GnRH neurons by activating opioid-receptor-like 1 receptor and G protein-coupled inwardly-rectifying potassium channels

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Abstract: Fertility relies on the integration of signals by gonadotropin-releasing hormone (GnRH) neurons, and the relay of this information to pituitary gonadotropes and gonads. Communication of GnRH neurons to gonadotropes occurs via pulsatile release of GnRH, with both amplitude and frequency of the GnRH pulses shaping the pituitary response. The kisspeptin neuronal subpopulation in the arcuate nucleus (ARC) is proposed to be the conductor of GnRH neurons' basal rhythm. However, kisspeptin triggers a long lasting excitation in GnRH neurons that needs to be silenced to shape secretory pulses. Here we investigate a circuit that could supply this regulation. Orphanin FQ/nociceptin (OFQ/N) is a neuropeptide related to the opioid family. It is found in proopiomelanocortin (POMC) neurons also in the ARC, known to influence GnRH neuronal activity. Two different models were used to examine the response of primary GnRH neurons to OFQ/N. In acute adult brain slices, OFQ(1-13)-NH2 (OFQ) inhibited GnRH neurons tagged with green fluorescent protein. The OFQ inhibition persisted after blockade of GABA- and glutamat- ergic inputs, indicating a direct action. OFQ also transiently reversed the kisspeptin-10 evoked excitation. RT-PCR showed that GnRH neurons maintained in explants expressed transcripts for the opioid-receptor-like 1 receptor (ORL1) and calcium imaging confirmed the direct inhibition of GnRH neurons by OFQ, mediated by ORL1. Pharmacological studies indicated that OFQ inhibition was subsequent to the activation of Gi protein coupling and G protein-coupled inwardly-rectifying potassium channels. Immunolabeling against OFQ/N highlighted fibers contacting GnRH neurons in mouse brain and POMC neurons in the ARC were immunolabeled for OFQ/N. POMC fibers contacted GnRH neurons and some POMC fibers in the preoptic area were co-labeled for OFQ/N. Together, these data provide a new inhibitory input from the ARC to GnRH neurons to potentially tune the strength of the kisspeptin ARC driven excitation of GnRH neurons.

Disclosures: S.S. Constantin: None. **S. Wray:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: NSF CAREER Award 1253126

Title: Embryonic exposure to bisphenol F affects development of GnRH neurons in the zebrafish

Authors: *S. RAMAKRISHNAN, K. WEILER
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Abstract: Bisphenols are widely used synthetic compounds that have been shown to exhibit estrogen-mimicking properties. While previous studies have shown that BPA exposure alters Gonadotropin Releasing Hormone (GnRH) neurons, the main controllers of reproduction and allied behaviors, there is limited knowledge on whether analogs of BPA (such as BPF, BPS) have similar effects or can be considered safe alternatives. The present study aims to address whether BPF has any impact on the developing GnRH system in the embryonic zebrafish. We used transgenic zebrafish embryos with GnRH3 neurons tagged with green fluorescent protein (GFP) allowing for easy visualization of GnRH neurons in both the terminal nerve (TN) and the preoptic area (POA). The TN-GnRH3 population is thought to link sensory information such as photoperiod and conspecific cues with reproduction, while the POA-GnRH3 population controls the hypothalamo-pituitary-gonadal axis. Zebrafish embryos were exposed to three different concentrations of BPF (50ug/L, 100ug/L, 200ug/L) from fertilization through 3 days post fertilization (dpf) and their GnRH3 neurons sizes were imaged using fluorescent microscopy. At 2dpf, embryos exposed to 50ug/L BPF showed a reduction in the area of both TN-GnRH3 neurons (44%) and POA-GnRH3 neurons (53%; $p<0.0001$) compared to vehicle-treated controls. However, 200ug/L BPF exposed embryos showed a 26% increase in TN-GnRH3 neuron area when compared to controls ($p<0.04$). No significant changes in eye size or body size were observed. BPF potentially targets GnRH neuron development in a non-monotonic manner.

Disclosures: S. Ramakrishnan: None. **K. Weiler:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: India Alliance Early Career Fellowship

Title: Estrogen and thyroid mediated regulation of the BDNF natural antisense transcript

Authors: *S. SHAH[1,2], P. TIWARI[1], D. MOAZED[2], V. A. VAIDYA[1]
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Abstract: A number of studies have implicated the role of hormones such as; glucocorticoids, thyroid hormones (T4, thyroxine; and T3, 3,5,3′-triiodo-l-thyronine) and gonadal steroids such as (estrogen (E2), progesterone(P4) etc.) in the regulation of cellular processes such as synaptic and structural plasticity and in the modulation of neurodevelopment and cognition. However, the

molecular targets of these neurohormones that predominantly exert their actions on receptors, that serve as transcription factors, is not well understood. Amongst the potential target genes is the neurotrophin, Brain Derived Neurotrophic Factor (BDNF). BDNF is known to regulate neuronal survival, maturation, differentiation in the developing brain, and continues to regulate plasticity in the mature brain. It is implicated in cognition, learning, memory and is thought to be involved in both the pathophysiology and treatment of mood disorders, such as depression. Previous studies indicate that BDNF expression is regulated by multiple neurohormones, including thyroid hormone and estrogen. Understanding the interplay between BDNF and neurohormones will aid in a deeper mechanistic understanding of hormone action in the brain. The BDNF gene comprises of multiple transcript variants, each governing local translation of the same BDNF protein. The mRNA transcript variants and alternate lengths of 3'UTR dictate differential spatial and temporal localization in neurons. The BDNF locus in humans comprises of a 190kb long Natural antisense transcript (NAT) that is alternately spliced and overlaps with the coding exon of BDNF. The mouse BDNF-NAT is much shorter and comprises of fewer splice variants. The levels of BDNF mRNA were found to negatively correlate with expression of BDNF-NAT. Interestingly, BDNF-NAT was found to be abundant in the ovaries and thyroid in humans. In our study we have sought to address the effect of T3 and E2 on BDNF-NAT expression. We find that the BDNF-NAT is regulated by, T3 and E2 *in-vitro* and *in-vivo*. A single injection of T3 in adult male mice, resulted in a gradual increase in BDNF-NAT levels whereas BDNF transcript variant levels decreased in the hippocampus. In-vitro treatment of hippocampal neurons with T3 also phenocopied the changes noted in vivo. Furthermore, we find that ovariectomy alters BDNF-NAT levels but not BDNF mRNA levels. We also find estrous cycle dependent changes in BDNF-NAT and mRNA levels. These results might suggest a potential role for BDNF-NAT in mediating the effects of hormones at the BDNF locus. Further experiments are underway to understand the mechanisms of this hormonal regulation of BDNF-NAT at this locus.

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Poster

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Topic: F.03. Neuroendocrine Processes

Support: OTKA K100722

K115984

Title: Proestrus evokes transcriptional changes in GnRH neurons and medial preoptic area of mice

Authors: *C. VASTAGH[1], N. SOLYMOSI[2], Z. LIPOSITS[1,3]
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Abstract: The pre-ovulatory GnRH surge release is triggered by estradiol (E2) during proestrus. The rising E2 level is sensed directly by GnRH neurons via estrogen receptor (ER) beta and by diverse estrogen receptive neuron assemblies of the brain that send afferents to GnRH neurons. Among them, the medial preoptic area (MPA) has a high significance due to its capability of processing estrogen signals and mediating information about the actual steroid milieu toward GnRH neurons via synaptic channels. The present study was undertaken to reveal the impact of proestrus on the expression of selected gene clusters in GnRH neurons and the MPA of regularly cycling GnRH-GFP transgenic mice. Laser capture microdissection (LCM) was used for harvesting GnRH neurons, while collection of MPA samples was assisted using mouse brain mold. The samples were collected from metestrous and proestrous mice, respectively between 16:00 and 18:00 h. The GnRH neuron pools were examined by Mouse Genome 430 PM Arrays and qPCR, while MPA samples were analyzed for selected genes using qPCR. In the MPA, as a chief integrator and mediator of the positive E2 feedback effect, differential expression of 24 genes reached significance ($p<0.05$). Genes upregulated in proestrus encoded neuropeptides (*Kiss1, Gal, Nt, Cck*), hormone receptors (*Ghsr, Oprm1*), gonadal steroid receptors (*Esr1, Pgr, Ar*), solute carrier family proteins (*Slc17a6, Slc18a2*), proteins of transmitter synthesis (*Th*) and transmitter receptor subunit (*Gria4*), and other proteins (*Ucp2, Nr4A2*). Proestrus evoked a marked downregulation of genes coding for *Adora2a, Slc32a1, Abat, Tac 1, Sort1, Cnr1, Epha3 and Aldh1l1*. With regards to transcriptional changes evoked in GnRH neurons by proestrus, we present the cluster of genes encoding neurotransmitter receptors. Differential gene expression was most apparent in GABA-ergic (*Gabbr1*, *Gabra3*, *Gabrb3*, *Gabrb2*, *Gabrg2*), glutamatergic (*Gria1*, *Gria2*, *Grin1*, *Grin3a*, *Grm1*, *Slc17a6*), cholinergic (*Chrnb2, Chrm4*), dopaminergic (*Drd3, Drd4*), adrenergic (*Adra1b*, *Adra2a*, *Adra2c*), adenosinergic (*Adora2a*, *Adora2b*), glycinergic (*Glra*), purinergic (*P2rx7*) and serotonergic (*Htr1b*) receptors. Collectively, the results indicate that proestrus evokes complex changes in the transcriptome of both GnRH neurons and the MPA and its footprint is clearly detectable on classical neurotransmitter signaling mechanisms onto GnRH neurons.

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Poster

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Science and Technology Research Promotion Program for Agriculture, Forestry, Fisheries and Food Industry from the Ministry of Agriculture, Forestry and Fisheries of Japan

Title: Stimulation of the GnRH pulse generator activity by peripheral administration of κ-opioid receptor antagonist in goats

Authors: *T. SASAKI[1], ***T. SASAKI**[1], D. ITO[1], T. SONODA[1], Y. WAKABAYASHI[2], T. YAMAMURA[2], H. OKAMURA[2], S. OISHI[3], T. NOGUCHI[3], N. FUJII[3], Y. UENOYAMA[1], H. TSUKAMURA[1], K.-I. MAEDA[4], F. MATSUDA[4], S. OHKURA[1]
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Abstract: Kisspeptin neurons in the hypothalamic arcuate nucleus (ARC) coexpress neurokinin B (NKB) and dynorphin A (Dyn), thus the neurons are referred to as KNDy neuron. KNDy neurons are considered to be a component of the GnRH pulse generator, because Dyn suppresses the GnRH pulse generator activity and NKB stimulates it. Antagonists to kappa-opioid receptor (KOR) and NKB receptor are, therefore, of use in controlling GnRH pulses and then gonadal activities. The present study examined the effect of oral administration of a KOR antagonist, PF-4455242, on pulsatile luteinizing hormone (LH) secretion in female Shiba goats to pursue the possibility of the antagonist to be used for artificial control of gonadal activities. Animals were fed with pelleted diet containing KOR antagonist (100 μmol/kg/day) for 7 days. The first day of oral administration was designated as Day 1. Blood samples were collected every 6 min for 4 h at Days 0, 2, 4, 7 and 9. Plasma LH concentrations were determined by radioimmunoassay. The oral administration of the KOR antagonist significantly ($p<0.05$, vs. control group) decreased inter-peak intervals of LH pulses on Day 7. We then examined the effect of intravenous injection of the antagonist on the multiple unit activity (MUA) recorded from the caudal ARC, an electrophysiological manifestation of the GnRH pulse generator activity. The MUA was monitored in ovariectomized estrogen-treated female goats (n=4) during the periods of 4-h intravenous infusion of the KOR antagonist (10 μmol/kg). Intravenous infusion of the KOR antagonist significantly increased the frequency of MUA volleys. Thus, it is most likely that the oral administration of the KOR antagonist stimulates LH pulses through the stimulation of GnRH pulse generator activity at the level of central nervous system. The oral administration of KOR antagonists would be a simple method to facilitate pulsatile LH secretion and consequently follicular growth in farm ruminants, such as cattle.

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Poster

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Topic: F.03. Neuroendocrine Processes

Support: JSPS KAKENHI Grant 15K14842, 16H05014, 16H06206

Title: Introduction of DREADDs in goat arcuate nucleus using adeno-associated virus

Authors: *R. TATEBAYASHI[1], Y. SUETOMI[1], K. KOBAYASHI[2], S. OHKURA[1], F. MATSUDA[3]
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Abstract: Background
Kisspeptin is the neuropeptide that stimulate gonadotropin-releasing hormone (GnRH) secretion. KNDy neurons, containing kisspeptin, neurokinin B and dynorphin A, in the arcuate nucleus are suggested to be the generator of pulse mode secretion of GnRH but the direct evidence is still not shown. Recently, chemogenetics has been emerged as a valuable method for clarifying the role of neurons. This technology, which uses designer receptors exclusively activated by designer drugs (DREADDs) and its specific ligand, enables to control the activity of targeted neurons. In the present study, we tried to express DREADDs in goat KNDy neurons to clarify the role of KNDy neurons as the GnRH pulse generator.
Materials and Methods
We used two recombinant adeno-associated viruses (AAV) for expressing DREADDs. One AAV contains Cre recombinase gene under the goat *TAC3* (neurokinin B gene) promoter. The other AAV contains a double-floxed inverted DREADD and mCherry genes driven by EF1α promoter. Firstly, we examined whether the co-introduction of these AAVs can express DREADDs in KNDy neurons in vitro. We transfected expression plasmids of these AAV into immortalized goat KNDy neuron cell line by electroporation. Two days after the electroporation, we observed fluorescence of mCherry. Next, we tried to express DREADDs in goat KNDy neurons in vivo. We inserted the injector to arcuate nucleus of castrated male goats and injected the 2 AAVs (1 μL of 1.0 x 10^9 vg/μL each). Three to four weeks later, the goats were perfused with 4% paraformaldehyde. Frozen sections of the hypothalamus were made and DREADD expression was detected by immunohistochemistry for mCherry.
Results and Discussion
Co-introduction of the AAV-expressing plasmids successfully expressed mCherry in the goat KNDy neuron cell line, suggesting that these AAVs can express DREADDs in KNDy neurons in vivo. In in vivo experiment, mCherry-immunoreactive cells were observed in the arcuate

nucleus, showing the capacity of these AAVs to express DREADDs in goat KNDy neurons. Together, these results suggested that chemogenetics are applicable to goat KNDy neurons to clarify the neuroendocrine mechanisms regulating reproduction in ruminants.

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Poster

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Topic: F.03. Neuroendocrine Processes

Support: Hungarian Scientific Research Fund (OTKA K100722 and K115984 for ZL)

Title: Stimulation of GnRH neurons by glucagon-like peptide-1 utilizes an activated nitric oxide and suppressed endocannabinoid retrograde signaling to presynaptic GABAergic bouton

Authors: *I. FARKAS[1], C. VASTAGH[1], E. FARKAS[2,3], F. BALINT[1,3], K. SKRAPITS[1], E. HRABOVSZKY[1], C. FEKETE[2,5], Z. LIPOSITS[1,4]
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Abstract: Glucagon-like peptide-1 (GLP-1), a metabolic signal molecule, regulates reproduction, although, the involved molecular mechanisms have not been elucidated, yet. Therefore, direct responsiveness of gonadotropin-releasing hormone (GnRH) neurons to the GLP-1 analog Exendin-4 and elucidation of molecular pathways acting downstream to the GLP-1 receptor (GLP-1R) in GnRH neurons have been studied. Loose patch-clamp recordings revealed that Exendin-4 (100 nM-5 μM) elevated firing rate in hypothalamic GnRH-GFP neurons of male mice via activation of GLP-1R. Whole-cell patch-clamp measurements demonstrated increased excitatory GABAergic miniature postsynaptic currents (mPSCs) frequency after Exendin-4 administration, which was eliminated by the GLP-1R antagonist Exendin-3(9-39) (1 μM). Intracellular application of the G-protein inhibitor GDP-beta-S (2 mM) impeded action of Exendin-4 on mPSCs, suggesting direct excitatory action of GLP-1 on GnRH neurons. Blockade of nitric-oxide (NO) synthesis by L-NAME (100 μM) or NPLA (1 μM) or intracellular scavenging of NO by CPTIO (1 mM) partially attenuated the excitatory effect of Exendin-4. Similar partial inhibition was achieved by hindering endocannabinoid pathway using CB1 inverse-agonist AM251 (1 μM). Simultaneous blockade of NO and endocannabinoid

signaling mechanisms eliminated action of Exendin-4 suggesting involvement of both retrograde machineries. Intracellular application of the TRPV1-antagonist AMG9810 (10 μM) or the FAAH-inhibitor PF3845 (5 μM) impeded the GLP-1-triggered endocannabinoid pathway indicating an anandamide-TRPV1-sensitive control of 2-AG production. Furthermore, GLP-1 immunoreactive axons innervated GnRH neurons in the hypothalamus suggesting that GLP-1 of both peripheral and neuronal sources can modulate GnRH neurons. RT-qPCR study confirmed the expression of GLP-1R and nNOS mRNAs in GnRH-GFP neurons. Immuno-electron microscopic analysis revealed the presence of neuronal nitric oxide synthase (nNOS) protein in GnRH neurons. These results indicate that GLP-1 exerts direct facilitatory actions via GLP-1R on GnRH neurons and modulates NO and 2-AG retrograde signaling mechanisms that control the presynaptic excitatory GABAergic inputs to GnRH neurons.

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Poster

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Title: Acute psychosocial stress alters LH pulses, kisspeptin neurons, and RFRP-3 neurons in mice

Authors: *J. A. YANG[1], R. A. PARRA[1], C. I. SONG[1], S. B. Z. STEPHENS[1], M. J. KREISMAN[1], D. J. HAISENLEDER[2], K. M. BREEN[1], A. S. KAUFFMAN[1]
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Abstract: Stress disturbs many physiological processes, including reproduction. While it is known that psychosocial stress inhibits several components of the hypothalamic pituitary gonadal (HPG) axis, including gonadotropin secretion, it is less clearly understood how stress regulates reproductive circuits in the brain. To test the effects of acute restraint stress, a psychosocial stress, on gonadotropin secretion, we first ovariectomized (ovx) female mice and exposed them to no stress (controls) or 90 min of restraint stress, during which time we measured

pulsatile circulating LH levels. LH pulse frequency and interpulse interval were significantly decreased in stressed animals compared to controls, with no effects on LH pulse amplitude. Next, to determine the effects of acute restraint stress on reproductive neuropeptides known to regulate GnRH neurons, we examined kisspeptin and RFRP-3 neurons, positive and negative regulators of the HPG axis, respectively. Female mice were ovx and separated into control (no stress) or 45, 90, or 180-min restraint stressed groups. *Kiss1 (*arcuate nucleus) and *Rfrp* (dorsal medial nucleus) expression and neuronal activation were examined using single and double-label *in situ* hybridization (ISH). Acute restraint stress had no effect on *Kiss1* mRNA levels, though there was a significant decrease in *Kiss1* neuronal activation at all time points, suggesting a decrease in stimulatory kisspeptin input to GnRH neurons. Furthermore, *Rfrp* levels increased after 180 min restraint stress. *Rfrp* neuronal activation was significantly increased after 45 min of restraint stress but not at later durations, suggesting that increased RFRP-3 signaling, known to inhibit GnRH and LH, may occur rapidly following acute stress. These data suggest that stress-induced suppression of the HPG axis in mice may be due, at least in in part, to regulation at levels upstream of GnRH neurons, either directly or indirectly, through *Kiss* and/or *Rfrp* neurons.

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Poster

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Title: Hypothalamo-pituitary-gonadal axis is transiently affected during experimental autoimmune encephalomyelitis in female dark agouti rats

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, more prevalent in women than in man. Here, we summarize the ongoing investigations on the effects of experimental autoimmune encephalomyelitis (EAE), an animal model of MS, on the hypothalamo-pituitary-gonadal axis, an issue not systematically

investigated in MS patients or in animal models of MS. The disease was elicited by intradermal injection of 150 µl suspension of spinal cord homogenate and Complete Freund's Adjuvans (CFA) to female Dark Agouti rats. Controls included the group of intact animals and the group of rats which were subjected to intradermal injection of CFA only. The symptoms, weight of the animals, and the stage of the estrous cycle were evaluated daily, from 9:00-10:00 AM. The first symptoms (disease onset, characterized by weight loss and flaccid tail) in immunized animals occurred after 8-10 days. The illness progressed to paralysis (peak of the disease), around day 14, and was resolved by day 28. The animals were sacrificed at the onset, peak, and at the end of the disease, in diestrus, under deep anesthesia. The blood was taken from the heart, serum was extracted, and luteinizing hormone (LH) was measured by ELISA. The pituitary and hypothalamic tissues were collected for qRT-PCR analaysis of expression of genes of interest. For immunohistochemistry, the whole brains were immersion fixed in 4% paraformaldehyde, cryopreserved and cut on cryotome. Our results indicate that, with the onset of the disease, animals stopped cycling; the cycle was arrested in diestrus, which persisted until recovery. Serum levels of LH were lower in EAE animals during the symptomatic phases of the disease, when compared to control and CFA treated group, but returned to normal levels in recovered animals. In addition, the expression level of GnRH receptor gene in the pituitary tissue was significantly lower at the peak of the disease, when compared to control and CFA group, as well as the expression of *Kiss1* gene in hypothalamus. Hypothalamic tissue of EAE animals also showed signs of inflammation, with increased gene expression of pro-inflammatory cytokines and increased gene and protein expression of glial fibrillary acidic protein. We hypothesize that EAE induces transient inflammation in the hypothalamus, which suppresses transcription of *Kiss1* gene and thus affects GnRH release, leading to a decay in GnRH receptor gene expression and LH synthesis and release and interruption of the estrous cycle. Further studies are needed to clarify whether EAE disrupts hypothalamo-pituitray-gonadal axis in males as well.

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Poster

160. HPG Axis

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

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Topic: F.03. Neuroendocrine Processes

Support: NRF-2017R1A2A1A05001351

DGIST 2017010095

Title: Light-induced activation of GnRH using kisspeptin neurons in two distinct hypothalamic nuclei

Authors: *D. KIM[1,2], J. KIM[1,3], I. PARK[1], S. JANG[1], M. CHOI[1], K. KU[1], G. SON[4], H. CHOE[1], K. KIM[1,5]
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Abstract: Kisspeptin, which is encoded by *Kiss1* gene, plays a crucial role in the regulation of mammalian reproduction by synchronizing gonadotropin-releasing hormone (GnRH) pulse generator. Mainly located in the arcuate nucleus (ARC) and the anteroventral periventricular nucleus (AVPV) in the hypothalamus, kisspeptin neurons are poised to generate GnRH pulse and surge. Our group previously reported that intermittent administration of kisspeptin elicits synchronization of GnRH promoter activity as well as pulsatile secretion of GnRH. However, it remains unknown what is the driving force for the pulsatile output of kisspeptin neurons. We hypothesized that transcriptional burst of *Kiss1* expression may drive the pulsatile secretion of kisspeptin. To address the hypothesis, we aimed to analyze the pulsatility of GnRH neurons when expression profile of *Kiss1* is controlled by light stimulation in a temporally precise manner. By using a light-inducible gene expression system (GAVPO-UAS), we developed constructs that can induce the expression of *Kiss1* or tyrosine hydroxylase (*TH*), which are co-expressed in AVPV kisspeptin neurons. Blue-light stimulation induced 4-fold increase of *TH* transgene expression in vitro. In order for kisspeptin neuron-specific expression, we utilized knock-in mouse line specifically expressing *Cre* under control of *Kiss1 cis* element *(Kiss1-IRES-Cre*). Slice cultures were established in order to contain GnRH neurons as well as kisspeptin neuronal cell bodies and axonal projections in one plane. Adeno-associated virus (AAV) encoding *Cre* recombinase-dependent GAVPO and AAV harboring UAS promoter followed by *Kiss1* were co-infected on *Kiss1-IRES-Cre* mice to examine the effect of kisspeptin neuron-specific gene expression. Using genetically encoded calcium indicator RCaMP, kisspeptin neuronal activation was detected upon light induction of *Kiss1* gene. We also investigated the differential effect of transcriptional burst in distinct kisspeptin neuronal populations. Light induction of *Kiss1* expression and analysis of its modulation on kisspeptin, and further GnRH neurons, would elucidate the mechanism underlying pulsatile kisspeptin secretion and help understand the genomic drive of the GnRH pulse generator.

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Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: Research Fellowship for Young Researchers, Japan Society for the Promotion of Science

Title: Suckling-induced changes in TIP39 and somatostatin expressions in the rat brain

Authors: *A. SUGIMOTO, Y. UENOYAMA, N. IEDA, K. IKEGAMI, N. INOUE, H. TSUKAMURA
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Abstract: Reproductive function is profoundly suppressed in lactating rats. The suppression is considered to be due to the suckling-induced inhibition of kisspeptin gene (*Kiss1*) expression in kisspeptin/neurokinin B/dynorphin A (KNDy) neurons in the arcuate nucleus (ARC). It has been reported that tuberoinfundibular peptide of 39 residues (TIP39) gene expression increased during lactation in the posterior intralaminar complex of the thalamus (PIL) and medial paralemniscal nucleus (MPL), and that TIP39-immunoreactied fibers projected to the ARC of lactating rats. Moreover, it is suggested that TIP39 may induce an increase in prolactin release in lactating rats. Our previous study found that TIP39 receptor gene (*Pth2r*) expression seemed to overlap with somatostatin gene (*Sst*) expression in the ARC of lactating rats. Since the somatostatin receptor is an inhibitory GPCR, we hypothesized that TIP39 and somatostatin (SST) neurons might be involved in the inhibition of ARC *Kiss1* expression during lactation. Thus, this study aims to examine the effects of suckling stimulus on TIP39 and SST expressions in the rat brain to explore the possibility that TIP39 and SST might participate in the ARC *Kiss1* suppression in lactating rats. To address this issue, the distributions of *Pth2r*, *Sst*, somatostatin receptor 2 gene (*Sstr2*) and neurokinin B gene (*Tac3*) were investigated in postpartum rats. Postnatal rats were divided to two groups: lactating dams with 8 pups and non-lactating dams without pups. All rats were ovariectomized on the postnatal day 2, and the brains were collected on day 8 to be subjected to *in situ* hybridization (ISH) for the above-mentioned genes. The number of TIP39 gene-expressing cells in the PIL and MPL, and of *Pth2r*-expressing cells in the dorsomedial part of the ARC and the medial amygdala nucleus were significantly higher in lactating rats compared to non-lactating rats. The number of *Sst*-expressing cells in the ARC was comparable between two groups, while it significantly increased in the PIL of lactating rats. Comparable number of *Sstr2*-expressing cells was found in the medial part of ARC in both groups. Double ISH for *Pth2r* and *Sst* showed that *Pth2r* signals expressed in 1.5% of ARC *Sst*-positive cells in lactating rats, while double ISH for *Sstr2* and *Tac3* showed that *Sstr2* signals were found in 0.9% of *Tac3*-expressing cells in the ARC. These results suggest that TIP39 neurons may innervate a few ARC SST neurons and that at least a few ARC KNDy neurons may be an action site of the SST. Taken together, the present results suggest that the suckling-induced increase in PIL and MPLTIP39 and ARC SST expressions may partially be involved in the ARC Kiss1 suppression during lactation.

Disclosures: A. Sugimoto: None. **Y. Uenoyama:** None. **N. Ieda:** None. **K. Ikegami:** None. **N. Inoue:** None. **H. Tsukamura:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: NIH Grant HD042635

Title: ERαΔ4, a splice variant of estrogen receptor-α, signals through mGluR2, *In vivo*

Authors: *A. M. WONG[1], A. K. SCOTT[1], P. E. MICEVYCH[2]
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Abstract: ERαΔ4 is a 52 kDa alternative splice variant of estrogen receptor alpha (ERα) missing exon 4 from ESR1 mRNA. The ERαΔ4 is present in plasma membrane fractions along with the full length ERα (65 kDa). In vitro, ERαΔ4 is trafficked to the plasma membrane and internalized when stimulated by estradiol. While the membrane presence of ERαΔ4 may be due to the absence of the nuclear localization sequence located in exon 4, previous work has shown that ERs are trafficked to the membrane in association with caveolin proteins. These caveolins also determine the metabotropic glutamate receptor that the ER will transactivate to signal. For example, ERα associates with caveolin-1 allowing an interaction with mGluR1a leading to stimulatory signaling (e.g., an increased release of internal calcium). To determine which caveolin and mGluR associate with ERαΔ4, co-immunoprecipitation experiments were done with the membrane fraction from the arcuate nucleus of the hypothalamus (ARH). ERαΔ4 did not associate with caveolin-1 or mGluR1a. However, ERαΔ4 co-imunoprecipitated with caveolin-3 and mGluR2. Caveolin-3 siRNA microinjection into female rat ARH reduced caveolin-3 protein by 50% and a 60% decrease in ERαΔ4 in membrane fractions. Full-length ERα levels were not changed on the membrane. Estradiol disrupted interactions between mGluR2 and caveolin-3 as demonstrated by a 40% decrease in mGluR2 and caveolin-3 co-immunoprecipitation after estradiol treatment. Since ERα interactions with mGluR2 inhibit cell signaling, as in DRG neurons, we examined whether ERαΔ4 mediated the estradiol decrease of kisspeptin expression in the ARH. Estradiol suppressed kisspeptin mRNA levels by 60%; however, a third ventricle injection of the mGluR2 antagonist, LY341,495 (10 µg) 30 min prior to EB, did not prevent the estradiol suppression of ARH kisspeptin expression. These results are consistent with immunocytochemical results that showed that mGluR2 was not colocalized with dynorphin, a co-transmitter in ARH kisspeptin neurons. At present, results suggest that ERαΔ4 negatively regulates cell signaling but does not appear to mediate estradiol's action in ARH kisspeptin neurons.

Disclosures: A.M. Wong: None. **A.K. Scott:** None. **P.E. Micevych:** None.

Poster

160. HPG Axis

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 160.17/OO26

Topic: F.03. Neuroendocrine Processes

Title: High-fat, high-sugar diet disrupts hormonal balance during preovulatory surge and induces polycystic ovaries

Authors: K. M. VOLK[1], J. A. ROBERTS[1], V. V. POGREBNA[2], J. E. ZACHRY[1], *S. BLYTHE[2], N. TOPORIKOVA[3]
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Abstract: Diet-induced obesity has been associated with the development of various reproductive deficits; however, the mechanism for the neuroendocrine control of ovulation by the diet remains unclear. To determine the effects of a high-fat, high-sugar (HFHS) diet on the preovulatory hormonal surge and ovarian morphology, female Sprague Dawley rats were weaned at p23 and randomly separated into two diet groups. The control group (n= 14) received *ad libitum* access to standard rat chow and water, and the HFHS group (n= 16) received a diet composed of 60% calories from fat, a 30% sucrose solution and water *ad libitum.* Serial and terminal blood samples were taken during the preovulatory gonadotropin surge and on diestrus 1, respectively. Radioimmunoassay was used to measure the concentration of LH, FSH, estradiol (E2), progesterone (P4), and testosterone (T). On average, the HFHS diet group exhibited a significantly lower progesterone surge on the evening of proestrus than the control group ($p< 0.05$). In contrast, there was a significantly increased level of estradiol in the HFHS diet group on the evening of proestrus. Surprisingly, LH levels did not follow this increase in estradiol. However, the HFHS diet group showed a significantly decreased basal LH level on diestrus 1 compared to the control group ($p< 0.05$). After sacrafice, ovaries were fixed, stained, and the number of cysts and corpora lutea (CL) were counted. The HFHS group had a significantly greater number of cysts, with a corresponding decrease in CL, suggestive of impaired fertility. Interestingly, we found an exponential relationship between the P4/T ratio on diestrus 1 and the number of cysts in the HFHS group. These data suggest that the HFHS rats exhibited both abnormal hormone levels and polycystic ovaries, which are common characteristics of polycystic ovary syndrome (PCOS). This implies that diet induced an alteration in the control of the hypothalamic-pituitary-gonadal (HPG) axis.

Disclosures: K.M. Volk: None. **J.A. Roberts:** None. **V.V. Pogrebna:** None. **J.E. Zachry:** None. **S. Blythe:** None. **N. Toporikova:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: NIH HD69702

Title: Glutamatergic leptin receptor expressing cells in the ventral premammilary nucleus facilitates reproduction

Authors: *N. BELLEFONTAINE, A. CARA, C. F. ELIAS
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Abstract: The adipocyte-derived hormone leptin is necessary for reproduction, where its primary action on fertility is exerted in the brain. The ventral premammiliary nucleus (PMv) of the hypothalamus is a critical region mediating leptin's control of reproduction. While the PMv is predominately glutamatergic, controversies exist to the relative contribution of leptin receptor (LepR) signaling in glutamatergic versus GABAergic neurons in regulating reproduction. Previous reports have shown that the deletion of LepR in cells expressing the glutamate transporter (VGLUT2, encoded by the *Slc17a6* gene) resulted in no obvious reproductive deficit. However, we have previously shown that LepR signaling in glutamatergic PMv neurons is sufficient for fertility. Using molecular genetic tools we sought to examine the function of LepR expressing glutamatergic cells in the PMv for reproductive physiology. To this aim, we selectively restored LepR in the PMv of mice otherwise null for LepR while concurrently deleting the glutamate transporter VGLUT2 ($LepR^{loxTB/loxTB}$; $VGLUT2^{loxP/loxP}$) through injection of an AAV-Cre directly into the PMv. Restoration of LepR in the PMv allowed for the progression of puberty in mice. However, in mice with the concurrent deletion of VGLUT2, no progression through puberty was observed, including vaginal opening and increased uterine size, indicating that glutamate transmission is involved in driving puberty. We next examined whether activation of LepR neurons in the PMv stimulates GnRH/LH release. To accomplish this, a Cre-dependent virus expressing the activating isoform of designer receptors exclusively activated by designer drugs (DREADDs) was injected into adult female LepR-Cre mice. PMv LepR-Cre cells expressing DREADDs were acutely activated by its ligand clozapine-N-oxide (CNO). We performed serial blood collection every 15 minutes over a one hour period following CNO infusion and observed a drastic increase in plasma LH levels, suggesting that PMv LepR neurons facilitate reproduction by influencing GnRH/LH release. We are currently assessing the role for glutamatergic neurotransmission in mediating the increase in GnRH/LH release following DREADD activation in LepR PMv neurons and downstream mechanisms using ontogenetic activation and electrophysiological recordings. Together, the data suggest glutamatergic

neurotransmission from the PMv are important for relaying leptin's signaling to the reproductive axis.

Disclosures: **N. Bellefontaine:** None. **A. Cara:** None. **C.F. Elias:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: NIH Grant HD041469

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Title: Ionotropic glutamatergic transmission to AVPV and arcuate kisspeptin neurons is differentially regulated by estradiol

Authors: ***L. WANG**[1], M. L. GREENWALD-YARNELL[4], M. G. MYERS, Jr.[2], S. M. MOENTER[3]
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Abstract: Gonadotropin-releasing hormone (GnRH) secretion controls fertility. Estradiol, via estrogen receptor α (ERα), feeds back to control GnRH and subsequent luteinizing hormone (LH) release. Low estradiol provides negative feedback; during the preovulatory stage, estradiol levels rise and its action switches from negative to positive to initiate GnRH/LH surges and trigger ovulation. Loss of ERα in glutamatergic neurons or blockade of ionotropic glutamate receptors in the hypothalamus blocks the LH surge. GnRH neurons receive limited glutamatergic inputs and do not express detectable ERα, we thus tested if glutamatergic inputs to two of their afferent populations, kisspeptin neurons in the anteroventral periventricular (AVPV) and arcuate nuclei, are regulated by estradiol. Spontaneous excitatory post-synaptic currents (EPSCs) to GFP-identified kisspeptin neurons were recorded in mouse brain slices (n/group ≥11 except KERKO n ≥7). We previously showed that during the proestrus phase of the cycle (positive feedback), EPSC frequency is increased in AVPV and decreased in arcuate kisspeptin neurons compared to diestrus (negative feedback). Here we show estradiol mediates these changes using ovariectomized mice ± estradiol replacement (OVX vs OVX+E, AVPV 1.6 ± 0.2 vs 3.8 ± 0.7 Hz, $p < 0.01$; arcuate 3.7 ± 0.4 vs 1.7 ± 0.2, $p<0.05$). This suggests estradiol feedback extends beyond AVPV and arcuate kisspeptin neurons to their glutamatergic inputs. We tested if ERα in kisspeptin cells is crucial for estradiol regulation of glutamatergic inputs to these cells by

recording EPSCs in kisspeptin-specific ERα knockout (KERKO) mice. In cells from KERKO mice, EPSCs frequency to AVPV neurons was decreased compared to control proestrous mice, which have similarly high estradiol levels (KERKO vs proestrus, 4.5 ± 0.5 vs 1.9 ± 0.5 Hz, p=0.01). EPSC frequency in arcuate neurons was markedly increased in cells from KERKO mice compared to control proestrous mice (KERKO vs proestrus, 8.7 ± 0.3 vs 3.2 ± 1.1 Hz, p <0.01). Further, EPSC frequency in kisspeptin neurons was not regulated by estradiol in KERKO mice (KERKO, OVX vs OVX+E, AVPV, 1.9 ± 0.3 vs 1.7 ± 0.2 Hz, p=0.9; arcuate, 5.6 ± 1.0 vs 6.8 ± 1.3 Hz, p=0.2). These observations suggest estradiol regulation of glutamatergic inputs to kisspeptin neurons requires ERα in kisspeptin cells. Arcuate kisspeptin neurons use glutamate as a neurotransmitter and project to both kisspeptin populations, thus may be one source of this transmission. Alternatively, kisspeptin neurons may regulate other glutamatergic inputs through local circuits. Future work will focus on identifying these glutamatergic inputs to extend the estradiol feedback network.

Disclosures: L. Wang: None. **M.L. Greenwald-Yarnell:** None. **M.G. Myers:** None. **S.M. Moenter:** None.

Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: Academy of Finland Grant 282926

Title: Selective depletion of kisspeptin signaling in oocytes causes premature ovarian senescence

Authors: *S. T. RUOHONEN[1,2], F. GAYTÁN[3,4], A. USSEGLIO GAUDI[1], M. POUTANEN[1,2], M. TENA-SEMPERE[3,4,2,1]
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Abstract: Kisspeptins, a family of structurally related peptides encoded by the *KISS1* gene, are mainly produced in the hypothalamus and crucial for the pre-ovulatory surge of gonadotropins and hence, ovulation. The Kiss1 receptor, Gpr54, is expressed in the hypothalamus and in target tissues, *e.g.* oocytes, where its role is not fully characterized. Our hypothesis is that kisspeptins acting on oocytes might modulate follicular dynamics and ovulation. Global Gpr54$^{-/-}$ mice are hypogonadotropic and infertile; female null mice display disrupted folliculogenesis and anovulation. However, despite the predominant brain actions of kisspeptins, how much of this

phenotype is due to local, and not central, kisspeptin signaling deficiency remains unknown. To address this, we generated a conditional oocyte-specific *Gpr54* deficient mouse line (OoGpr54$^{-/-}$), by crossing Gdf9-Cre^{+} mice with Gpr54$^{loxP/loxP}$ mice. The efficacy of Gdf9-promoter to drive the expression of Cre in oocytes was verified by a breeding test, and the *Gpr54* expression levels in different tissues were confirmed with qPCR. OoGpr54$^{-/-}$ mice were studied around puberty (PND35), and at 3-4 months of age. At the time of pubertal transition, OoGpr54$^{-/-}$ females were indistinguishable from their controls, as they entered into puberty, completed ovulation and began cycling. Preliminary results also suggest that 2-month-old OoGpr54$^{-/-}$ females are fertile and able to give birth to normal-sized litters. Three consecutive pregnancies have been followed so far, and will be continued for up to 1 year. At 3-4 months of age, macroscopic evaluation of the gonads and tissue weighing revealed no overt differences between genotypes (virgin females). Notwithstanding, already at this early age, the ovaries of OoGpr54$^{-/-}$ mice showed histological features reminiscent of premature aging, *i.e*. abundant atretic follicles and absence of healthy mature (pre-ovulatory) follicles and corpora lutea. However, the penetrance of this phenotype appeared to be incomplete at this age, so that only 8 out of 15 (55%) of OoGpr54$^{-/-}$ mice did display features of complete premature ovarian insufficiency (POI) accompanied with abnormal cycling profile. Interestingly, OoGpr54$^{-/-}$ females with normal ovarian morphology, showed increased hypothalamic levels of *Gpr54*. Additional analyses in OoGpr54$^{-/-}$ mice, targeting an older age (6 months), are currently on-going to further define the penetrance and precise time-window for instauration of the phenotype of POI in females with selective ablation of kisspeptin signaling in oocytes.

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Poster

160. HPG Axis

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Topic: F.03. Neuroendocrine Processes

Support: OTKA 112669 to EH

NAP-2 to EH

Title: Anatomical evidence indicates that reproductive aging of human males coincides with enhanced kisspeptin output by neurokinin B fibers

Authors: *E. HRABOVSZKY[1], A. CSEPREGI[1], B. A. BORSAY[2], K. RACZ[2], K. SKRAPITS[1]
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Abstract: Kisspeptin (KP) and neurokinin B (NKB) are synthesized by partially overlapping neuronal populations in the arcuate nucleus. These neurons have been implicated in pubertal development, negative sex steroid feedback and pulsatile gonadotropin-releasing hormone (GnRH)/luteinizing hormone (LH) secretion. The degree of overlap in cell bodies varies with age and sex, being significantly higher in arbitrarily defined 'aged' (50-67 yr) *vs.* 'young' (21-49 yr) men and in postmenopausal women (> 55 yr) *vs.* aged men. In this study we aimed to determine how reproductive ageing in men influences the extent of neuropeptide colocalization in the axonal compartment which is critical for efferent neuronal signaling. Immunofluorescent labeling of KP and NKB was followed by the quantitative analysis of their colocalization pattern in axon varicosities in groups of young *vs.* aged men. The extent of colocalization was found to be much higher in the cell bodies than in the axon varicosities, indicating that neurons capable of synthesizing both peptides utilize them differentially for efferent neuronal communication. Both KP and NKB fiber densities were increased in aged men and KP fiber numbers increased more robustly. While the density of single-labeled NKB fibers did not change and the density of single-labeled KP axons increased only slightly, there was a robust increase in the number of KP/NKB dual-immunoreactive axons. This was caused primarily by the 4.5-fold enhancement in the percentage of NKB axons that also expressed KP signal. These observations suggest that KP has a largely increased contribution to the neuropeptide output of KP and NKB neurons in aged men. The new occurrence of KP in a large subset of NKB perikarya and axons may be explained by epigenetic mechanisms causing transcriptional derepression of the KISS gene when testosterone negative feedback declines gradually with ageing. It will require clarification how the altered neuropeptide balance in KP and NKB axons changes the GnRH/LH pulse generator function.

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Poster

161. Thirst and Water Balance

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Klingenstein-Simons Fellowship Award

California Institute of Technology Startup Fund

Title: Neural circuits underlying fluid homeostasis

Authors: *V. M. AUGUSTINE[1], S. LEE[2], S. K. GOKCE[3], B. WANG[3], C. LOIS[3,2], Y. OKA[1,3,2]
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Abstract: Fluid homeostasis is essential for survival. Recent rodent studies have shown that the excitatory neurons within the lamina terminalis, composed of the subfornical organ (SFO), median preoptic nucleus (MnPO) and the vascular organ of the lamina terminalis (OVLT) induce drinking in water deprived states. However, the organization of the underlying circuit architecture is unknown. Using viral and electrophysiological circuit tracing techniques, we show that there are dense connections between specific subpopulations of the SFO, MnPO and OVLT. Furthermore, cell type specific acute inhibition and lesioning experiments revealed that there is a hierarchial organization of circuits within the lamina terminalis. With a chemogenetic approach, we show the necessity of a specific neural population for integrating and processing thirst signals from the lamina terminalis. Taken together, our results map out the primary thirst neural architecture and form the basis to study the computations underlying thirst.

Disclosures: V.M. Augustine: None. **S. Lee:** None. **S.K. Gokce:** None. **B. Wang:** None. **C. Lois:** None. **Y. Oka:** None.

Poster

161. Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

Support: OCAST HR 12-196

Title: Astrocyte immunolabeling in the dorsal vagal complex of female rats after furosemide treatment

Authors: *S. L. CORE[1], K. S. CURTIS[2]
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Abstract: Astrocytes interact with neurons to influence signaling in central areas involved in body fluid balance. The dorsal vagal complex (DVC), comprised of the area postrema (AP) and the nucleus of the solitary tract (NTS), is an initial sensor of visceral and chemosensory input

with a rich population of astrocytes. Estradiol alters behavioral and physiological responses to a number of body fluid challenges, but little is known about whether estradiol modulates astrocytes in the dorsal vagal complex. We hypothesized that signals associated with sodium loss affect astrocytes in the dorsal vagal complex which, in turn, influence central signaling important for compensatory responses, and that this effect may be altered by estradiol. The natriuretic-diuretic, furosemide, increases urinary sodium loss within an hour after treatment but an 18-24 hour delay typically transpires before rats consume sodium solutions. Thus, we assessed the effect of estradiol on furosemide-induced water and salt intake, and on levels of astrocytes in the DVC after furosemide. Adult female Sprague Dawley rats were ovariectomized under pentobarbital anesthesia (Pbt), allowed 7 days recovery, then given estradiol benzoate (EB; 10 μg/0.1 ml sesame oil, s.c.) or sesame oil vehicle (OIL; 0.1 ml, s.c.) on day one and two of a 4-day regimen. Rats were given two s.c injections 1-hour apart of 0.15 M NaCl (ISO; 1.0 mL/kg bw) or furosemide (5 mg/kg bw) in one of two protocols. In the short-term protocol, one hour after the 2nd injection, rats were given a 3-hr 2-bottle test (0.5 M NaCl and water) or were anesthetized with Pbt and perfused with paraformaldehyde. Brains were removed and cut in 40 μ sections. In the long-term protocol, rats were returned to their cages for 18 hours after the 2nd injection, and then treated as described. For immunolabeling, free-floating sections were labeled for a marker of astrocytes, glial fibrillary acidic protein (GFAP; Millipore; 1:10,000). Rats consumed 0.5 M NaCl after furosemide in the long-term, but not the short-term protocol, and EB enhanced 0.5 M NaCl intake. GFAP immunolabeling decreased after furosemide treatment in the long-term protocol in the AP and subadjacent NTS. In addition, the decrease in GFAP immunolabeling occurred more rapidly in EB-treated rats. Thus, changes in GFAP immunolabeling may be related to the furosemide-induced salt intake and the more rapid decrease in GFAP may be associated with EB enhancement of salt intake, suggesting a role for astrocytes in the DVC in behavioral responses to established sodium loss and/or volume loss. All procedures were approved by the Oklahoma State University Center for Health Sciences Animal Care and Use Committee.

Disclosures: S.L. Core: None. **K.S. Curtis:** None.

Poster

161. Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

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Title: Neural mechanism for presystemic regulation of vasopressin release

Authors: *A. KIM[1,2], Y. MANDELBLAT-CERF[2], J. MADARA[2], M. L. ANDERMANN[1,2], B. B. LOWELL[1,2]
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Abstract: Vasopressin (VP), an antidiuretic hormone, is key for maintaining water balance. VP release is regulated by two temporally distinct signals: 1) slow systemic signals that convey information about systemic osmolality, and 2) rapid 'presystemic' signals that anticipate future osmotic challenges. We recently demonstrated that VP neurons show bidirectional anticipatory presystemic responses to feeding and drinking. To find the source of presystemic regulation, we used rabies and ChR2-assisted circuit mapping to map afferents to neuroendocrine VP neurons. Major inputs to VP neurons come from the three sites in the Lamina terminalis, namely, SFO, MnPO and OVLT, and they provide mainly excitatory inputs. Using fiber photometry, we found that SFO^{Vglut2} and $MnPO^{Vglut2}$ neurons, like VP neurons, are rapidly inhibited by water-predicting cues and water intake. Inhibition of MnPO significantly attenuated the presystemic response of VP neurons to water cues and drinking while leaving the feeding-related presystemic response intact. These results suggest that water- versus food-related presystmic regulation are mediated by distinct neural pathways and MnPO functions as a gateway in water-related presystemic regulation of VP release.

Disclosures: A. Kim: None. **Y. Mandelblat-Cerf:** None. **J. Madara:** None. **M.L. Andermann:** None. **B.B. Lowell:** None.

Poster

161. Thirst and Water Balance

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Program#/Poster#: 161.04/OO34

Topic: F.09. Thirst and Water Balance

Title: Age, but not ovarian hormones, alters astrocyte density in the subfornical organ of female rats

Authors: *Z. D. SIMSEK[1], R. L. THUNHORST[2], A. K. JOHNSON[2], B. XUE[2], T. BELTZ[2], K. S. CURTIS[1]
[1]Pharmacol. and Physiol., Oklahoma State Univ., Broken Arrow, OK; [2]Dept Psychology, Univ. of Iowa, Iowa City, IA

Abstract: Forebrain sensory circumventricular organs--subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT)--have incomplete blood brain barriers and receptors for hormones associated with body fluid regulation. The circulating hormone angiotensin II acts on these circumventricular organs to regulate renal, cardiac, and vascular physiology, as well as behaviors related to body fluid balance. Astrocytes contribute to the blood brain barrier and may alter the excitability of cells that detect circulating angiotensin. Sex- and age-related differences in behavioral and central responses to angiotensin II have been reported; however, changes in astrocytes in the SFO and OVLT with elevated angiotensin II have not been examined in aged female rats. In this study, we used the β-adrenergic agonist Isoproterenol, which increases angiotensin II, to assess the effects on astrocytes in these circumventricular organs in female rats, and to determine whether any changes are modified by age. We used young (5 months old) and aged (25 months old) female Brown Norway rats that were ovariectomized and allowed to recover before sc injection with Isoproterenol (30 µg/kg) or 0.15 M NaCl vehicle. Ninety minutes later, rats were deeply anesthetized with pentobarbital and then perfused with paraformaldehyde. Brains were removed and sectioned at 40µm using a cryostat before immunohistochemical labeling of glial fibrillary acidic protein (GFAP; Millipore, 1:6000), a marker of astrocytes. Isoproterenol did not affect astrocyte labeling in the OVLT or SFO in either age group. However, the density of astrocytes in the SFO was greater in aged female rats. This change was independent of ovarian hormone depletion and suggests that, in female rats, age may alter astrocyte density in the SFO, and thereby impact either the detection of angiotensin II, or angiotensin II-induced excitability of neurons in this area.

Disclosures: Z.D. Simsek: None. **R.L. Thunhorst:** None. **A.K. Johnson:** None. **B. Xue:** None. **T. Beltz:** None. **K.S. Curtis:** None.

Poster

161. Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

Support: NIH Grant DK107500

Title: Associative learning contributes to the increased water intake observed after daily injections of angiotensin II

Authors: M. POSTOLACHE[1], H. R. JEAN[2], J. SANTOLLO[3], *D. DANIELS[1]
[1]Dept. of Psychology, [2]Dept. of Biol. Sci., Univ. At Buffalo - SUNY, Buffalo, NY; [3]Univ. of Kentucky, Lexington, KY

Abstract: Daily injections of angiotensin II (AngII) cause a progressive increase of water intake that resembles a classically ascribed non-associative sensitization. In previous attempts to uncover the neurobiological changes underlying this response, we tested for related changes in the AngII type 1 receptor (AT1R). These experiments, however, found only a small change in AT1R binding associated with the sensitizing treatment protocol, and the change was isolated to a limited region of the caudal portion of the tissue adjacent to the anteroventral third ventricle (AV3V). Moreover, the treatment associated with an increase in drinking resulted in a surprising decrease in receptor binding, an effect more commonly associated with desensitization than with sensitization. The present studies further probed the effect by attempting to isolate the AngII-receptor interaction from the drinking behavior by implementing a delay in water access after injection of AngII (icv) on four consecutive 'induction days.' On a fifth day ('test day'), we measured water intake when rats were allowed to drink immediately after AngII. The delay in water access effectively reduced water intake on the four induction days, and rats with longer delays in access (1 h or 3 h) drank less on the test day than did rats allowed to drink immediately after AngII on the induction days ($p < 0.05$), suggesting that the change in behavior resulted from a conditioned appetition, rather than from sensitization. Additional experiments ruled out a role for a conditioned drinking response to the injection alone, and demonstrated a lack of conditioned appetition after pairing injections of AngII with water given by intragastric catheter. Furthermore, preliminary findings indicate that MK-801 prevents the increase in intake normally observed in rats treated with AngII and given immediate access to water. Taken together, these findings suggest that the increased drinking observed after daily injections of AngII is a conditioned appetition resulting from repeated pairings of AngII and water intake. Furthermore, the effect appears to be mediated, at least in part, by NMDA receptor activation, which plays an important role in associative learning.

Disclosures: M. Postolache: None. **H.R. Jean:** None. **J. Santollo:** None. **D. Daniels:** None.

Poster

161. Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

Support: Marsden Fund, Royal Society of New Zealand

Title: Regulation of supraoptic nucleus vasopressin neuron activity by TRPV in lactating rats

Authors: *A. J. SEYMOUR, R. A. AUGUSTINE, C. H. BROWN
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Abstract: The antidiuretic hormone vasopressin is synthesised by vasopressin neurons in the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus. Vasopressin neurons are osmosensitive and detect changes in extracellular fluid osmolality via transient receptor vanilloid (TRPV) channels. Activation of TRPV channels increases vasopressin neuron activity, causing vasopressin secretion, which enhances water reabsorption from the kidney. During pregnancy and lactation, the osmotic set point is reduced so that body water is retained to aid development of the fetus, and prepare the mother for lactation. While it is known that altered vasopressin secretion during pregnancy and lactation resets osmolality, it is unclear how the threshold for vasopressin secretion is changed.
We obtained extracellular single unit electrophysiological recordings *in vivo* on anaesthetised female virgin and lactating rats. We exposed the ventral surface of the right SON using transphyrangeal surgery. A recording electrode was inserted into the SON and stimulation of the pituitary stalk to elicit antidromic spikes allowed identification of magnocellular neurons. Cholecystokinin was administered through an intravenous cannula to distinguish oxytocin and vasopressin neurons, as peripheral cholecystokinin excites oxytocin neurons, but inhibits, or has not effect on vasopressin neurons. We administered the TRPV antagonist ruthenium red to the SON via a microdialysis probe for up to 1 h. Ruthenium red reduced the firing rate of vasopressin neurons to a similar extent in virgin rats ($n = 11$) and lactating rats ($n = 8$; main effect of reproductive status, $P = 0.81$, main effect of time, $P < 0.001$, two-way repeated measures ANOVA), despite osmolality being ~ 10 mosmol kg^{-1} lower in lactating rats compared to virgin rats ($P < 0.01$, Student's *t*-test).
Our results suggest that although osmolality is lower during lactation, activation of TRPV channels on vasopressin neurons is similar in both virgin and lactating rats. Therefore, increased TRPV activation at lower osmolality during lactation might lower the threshold for vasopressin secretion, resulting in increased water retention in pregnancy and lactation.

Disclosures: A.J. Seymour: None. **R.A. Augustine:** None. **C.H. Brown:** None.

Poster

161. Thirst and Water Balance

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Topic: F.09. Thirst and Water Balance

Support: CIHR grant FDN-143337

Title: Salt loading promotes synchronization of phasic firing in vasopressin neurons of the rat supraoptic nucleus

Authors: *Z. S. THIROUIN[1], K. Y. CHOE[1], C. W. BOURQUE[2]
[1]Neurol. and Neurosurg., CRN / McGill Univ., Montreal, QC, Canada; [2]Neurol. and Neurosurg., CRN / Res. Inst. of the MUHC, Montreal, QC, Canada

Abstract: The antidiuretic hormone vasopressin (VP) is synthesized by magnocellular neurosecretory cells located in the hypothalamic paraventricular and supraoptic nuclei (SON) which project axons to the neurohypophysis. VP neurons increase their action potential firing rate in proportion with extracellular fluid osmolality to progressively increase VP secretion into the bloodstream. Under pronounced hyperosmotic conditions the electrical activity of these neurons changes to a type of bursting pattern named "phasic", where groups of spikes are interspersed by silent pauses (each lasting >1 s) to facilitate VP release (Poulain & Wakerley, 1982). In acute hypertonic conditions *in vivo*, spontaneous phasic activity is asynchronous among VP cells. Interestingly, another type of bursting can also be observed in VP neurons under hyperosmotic conditions. This activity, termed clustering, features briefer bursts and higher intraburst spiking frequency when compared with phasic firing. However, it remains unknown whether clustering is synchronous or asynchronous between VP neurons. Paired extracellular recordings performed in superfused hypothalamic explants confirmed that phasic firing is asynchronous between VP cells. However, recordings from SON neurons in explants prepared from salt loaded rats displayed a high degree of synchronization between bursts. The basis for this effect remains to be determined.

Disclosures: Z.S. Thirouin: None. **K.Y. Choe:** None. **C.W. Bourque:** None.

Poster

161. Thirst and Water Balance

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 161.08/PP2

Topic: F.09. Thirst and Water Balance

Title: Changes in gene expression of thyrotropin-releasing hormone (TRH) and its receptor during de- and re-hydration in the hypothalamus of neonatal layer chicks

Authors: *S.-I. KAWAKAMI
Hiroshima Univ. Grad. Sch. of Biosphere Sci., Hiroshima, Japan

Abstract: Thyrotropin-releasing hormone (TRH) is a neuroendocrine tripeptide which is mainly synthesized in the hypothalamus and regulates thermogenesis in the hypothalamus-pituitary-thyroid axis. We have previously reported that intracerebroventricular administration of TRH significantly inhibits cumulative water consumption without affecting feed intake, and TRH-immunopositive neurons are located in the various hypothalamic nuclei in neonatal chicks. The aim of the present study is, therefore, to examine gene expression of TRH and its receptor (TRH-

R) during de- and re-hydration in the hypothalamus of neonatal layer chicks. In the experiment 1, the chicks were free access to feed and divided into 4 experimental groups as follows: 1) free access to water (n=6), 2) dehydrated for 6 hr (n=8), 3) dehydrated for 12 hr (n=8), and 4) rehydrated for 1 hr after 12 hr-dehydration (n=7). In the experiment 2, to remove the effect of feed consumption on gene expression, the chicks were divided into 6 experimental groups as follows: 1) free access to feed and water (n=6), 2) free access to water without feed (n=5), 3) dehydrated for 12 hr without feed (n=7), 4) rehydrated without feed for 1 hr after 12 hr-dehydration (n=7), 5) rehydrated without feed for 2 hr after 12 hr-dehydration (n=7), and 6) rehydrated without feed for 4 hr after 12 hr-dehydration (n=7). After the treatments, the brain blocks containing hypothalamus were collected, and total RNA was extracted from the blocks and reverse-transcribed to cDNA to be subjected to real-time PCR analysis. Gene expressions of TRH, TRH-R, angiotensinogen (AGT), angiotensin receptor type 1 (AT1-R), and angiotensin receptor type 2 (AT2-R) were determined in the experiment 1, and of TRH and TRH-R in the experiment 2. In the experiment 1, the gene expression level of TRH significantly decreased after dehydration for 12 hr, and significantly increased after rehydration for 1 hr. The levels of AT1-R and AT2-R significantly increased after dehydration for 6 hr. In the experiment 2, the gene expression level of TRH significantly increased in free access to water without feed, decreased in dehydration for 12 hr without feed, and recovered to basal levels by rehydration. The changes of the levels of TRH-R were similar to those of TRH. These data suggest that TRH plays an essential role in the control of water intake in the brain of neonatal chicks.

Disclosures: S. Kawakami: None.

Poster

162. Motivation: Social Communication

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.01/PP3

Topic: G.02. Motivation

Support: NIMH R01MH102456

Title: Recruitment of the ventral tegmental area and its afferent pathways during socially rewarding behavior in juvenile male and female rats

Authors: *C. J. REPPUCCI[1], C. K. GERGELY[2], N. F. NASCIMENTO[2], G. S. RO[2], R. BREDEWOLD[1], A. H. VEENEMA[1]
[1]Neurosci. Program; Dept. of Psychology, Michigan State Univ., East Lansing, MI; [2]Dept. of Psychology, Boston Col., Chestnut Hill, MA

Abstract: The ventral tegmental area (VTA) is an essential component of the mesocorticolimbic dopamine reward system and an important node of the Social Decision-Making Network

(O'Connell & Hofmann, 2011). As such, the VTA is interconnected with brain regions implicated in the expression of social play, a highly rewarding behavior predominately displayed by juveniles, and expressed by nearly all mammalian species. In the current study, we investigated the recruitment of the VTA (Experiment 1) and its afferents (Experiment 2) during social play behavior in juvenile male and female rats. Single-housed juveniles were exposed, in their home cage, to an age- and sex-matched unfamiliar juvenile for 10 min ("Play" condition) or received similar handling but no partner ("No Play" condition). In Experiment 1, Fos and tyrosine hydroxylase (TH) immunohistochemistry was used to determine activation of the VTA and its dopaminergic neurons in response to social play. Preliminary data showed that females in the play condition had more Fos in the rostral VTA than females in the no play condition, and the opposite pattern was observed in males. No sex difference or effect of social play was found for Fos expression within TH-positive VTA neurons, which may have been due to the very low number of double-labeled neurons observed. In Experiment 2, we combined retrograde tract tracing using cholera toxin B subunit (CTB) with Fos immunohistochemistry to determine activation of afferent projections to the VTA in response to social play. Preliminary data showed that exposure to social play was associated with increased Fos induction in the medial prefrontal cortex (mPFC) and lateral septum (LS) for both sexes. Social play also induced Fos expression in CTB-positive neurons within these brain regions, but the occurrence of double-labeled neurons was very low. Together, these data suggest that social play is associated with weak VTA dopaminergic activation, as well as weak recruitment of mPFC and LS pathways to the VTA. However, the sex-specific activation of VTA non-dopaminergic neurons, and activation of the mPFC and LS in both sexes may serve as important clues for further investigation of the neural circuitry underlying social play behavior in juvenile males and females.

Disclosures: C.J. Reppucci: None. **C.K. Gergely:** None. **N.F. Nascimento:** None. **G.S. Ro:** None. **R. Bredewold:** None. **A.H. Veenema:** None.

Poster

162. Motivation: Social Communication

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.02/PP4

Topic: G.02. Motivation

Title: Vasopressin and oxytocin in the social behavior neural network: How to fiber projections and receptors compare?

Authors: *C. J. SMITH[1], B. T. DIBENEDICTIS[2], A. H. VEENEMA[3]
[1]Boston Col., Chestnut Hill, MA; [2]Boston Univ., Boston, MA; [3]Michigan State Univ., East Lansing, MI

Abstract: Vasopressin (AVP) and oxytocin (OXT) regulate social behavior by acting at their centrally expressed receptors, namely the AVP V1a receptor (V1aR) and the OXT receptor (OTR), respectively. Intriguingly, recent studies have provided evidence that AVP can mediate its behavioral effects through the OTR and OXT can mediate its behavioral effects through the V1aR. Based on these findings, we hypothesized that there would be anatomical overlap in the brain between AVP fiber projections and OTR expression and OXT fiber projections and V1aR expression. Moreover, AVP and OXT systems in the brain show neuropeptide-specific sex and age differences. Therefore, we further hypothesized that such sex and age differences would exist across AVP and OXT systems in those brain regions showing anatomical overlap between the two systems. To test these hypotheses, we compared AVP and OXT fiber densities (using immunohistochemistry) with V1aR and OTR binding densities (using receptor autoradiography) in adult and juvenile male and female rats across nodes of the social behavior neural network (SBNN). These nodes consist of the medial amygdala (MeA), posterior bed nucleus of the stria terminalis (BNSTp), lateral septum (LS), medial preoptic area (MPOA), ventromedial hypothalamus (VMH), anterior hypothalamus (AH) and the periaqueductal grey (PAG). We found that (i) there is often a lack of correspondence between fiber and receptor expression within AVP and OXT systems (e.g., OTR binding is dense in the VMH, while OXT fibers are sparse), (ii) there is often correspondence between high fiber and high receptor expression across AVP and OXT systems (e.g., AVP fibers and OTR binding are both dense in the MeA), and (iii) similar sex and age differences are observed for fiber and receptor expression across AVP and OXT systems (e.g., AVP fiber density and OTR binding density in the MeA and pBNST are higher in males and higher in adults). Together, these findings provide neuroanatomical evidence for overlap in fiber projections and receptor expression across AVP and OXT systems within nodes of the SBNN and reveal that this overlap changes in corresponding ways with sex and age. While further studies are warranted, we predict that AVP and OXT systems are mechanistically and functionally linked, which may have important implications for sex- and age-specific neuropeptide regulation of social behavior.

Disclosures: C.J. Smith: None. **B.T. DiBenedictis:** None. **A.H. Veenema:** None.

Poster

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Topic: G.02. Motivation

Support: NIMH R01MH102456

Title: Vasopressin in the lateral septum modulates sex-specific neurotransmission: Implications for sex-specific regulation of social play

Authors: *R. BREDEWOLD[1,2], J. K. SCHIAVO[2], A. H. VEENEMA[1,2]
[1]Dept. of Psychology, Michigan State Univ., East Lansing, MI; [2]Psychology, Boston Col., Chestnut Hill, MA

Abstract: Social play is an affiliative and rewarding behavior displayed by nearly all mammals and peaks during the juvenile period. We recently showed that arginine vasopressin (AVP) acting via the V1a receptor (V1aR) in the lateral septum (LS) regulates social play in opposite directions in male and female juvenile rats. The LS is often conceptualized as a relay station that receives input from many brain regions and is a core hub in the social decision-making network. Therefore, we sought to determine whether and how the LS-AVP system interacts with the release of a wide array of neurotransmitters (NTs) including GABA, glutamate (Glu), dopamine (DA), noradrenaline (NE), acetylcholine (ACh) and glycine and whether this occurs in sex-specific ways.
We used microdialysis with and without retrodialysis to quantify extracellular NT release in the LS in awake and freely moving juvenile rats, while 1) AVP was applied into the LS, 2) rats were exposed to social play or 3) a V1aR antagonist was administered into the LS.
We observed a variety of dynamic release patterns of NTs that were sex-, and condition-specific. In detail, application of AVP into the LS caused an increase in the extracellular Glu and DA release in the LS of females, while no change was seen in males. Other NTs did not change in sex-specific ways in response to AVP. Furthermore, exposure to social play was associated with an increase in the release of all NTs in females, while in males, DA and NE remained unchanged. Additionally, a sex difference was found in the absolute levels of extracellular Glu release in the LS, with higher levels in males than in females, under baseline conditions, after AVP administration and during social play. Finally, application of a V1aR antagonist in the LS caused sex differences in the extracellular release of Glu, NE and ACh, with higher release in females. Interestingly, the observed sex differences in extracellular Glu and DA release in the LS after AVP administration and during social play were eliminated with V1aR antagonist administration.
These findings suggest a differential involvement of NTs in the LS of male and female juvenile rats exposed to social play, with potential roles of Glu and DA in the sex-specific regulation of social play by the LS-AVP system.
This research was supported by NIMH R01MH102456 to AHV

Disclosures: R. Bredewold: None. **J.K. Schiavo:** None. **A.H. Veenema:** None.

Poster

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Topic: G.02. Motivation

Support: NSF IOS1253386 to AHV

Title: Behavioral and neuroanatomical characterization of the vasopressin system in the bed nucleus of the stria terminalis reveals potential coordination of separate populations of vasopressin neurons in mediating social behavior

Authors: *J. A. SMITH, R. BREDEWOLD, C. J. REPPUCCI, A. H. VEENEMA
Psychology, Michigan State Univ., East Lansing, MI

Abstract: Distinct populations of vasopressin-synthesizing neurons have diverse functions ranging from hydromineral homeostasis to social behavior. However, the potential for separate populations of vasopressin neurons to interact and coordinate social behavior is unclear. One population of neurons located in the posterior aspect of the bed nucleus of the stria terminalis (pBNST) both produce vasopressin and receive vasopressinergic inputs making the pBNST an ideal candidate region for exploring such interactions. Because the number of vasopressin neurons in the pBNST of males is androgen-dependent and increases with sexual maturity, we hypothesized that vasopressin signaling in the pBNST would be an integral part of mediating socio-sexual motivation. Utilizing a three-chamber testing apparatus, adult male rats were allowed to investigate a confined male or estrus female following microinjection of a vasopressin (V1a) receptor antagonist or vehicle into the pBNST. Blocking V1a receptors in the pBNST resulted in an attenuation of both female investigation and time spent in the female chamber compared with vehicle-treated rats. In contrast, blocking V1a receptors in the pBNST had no effect on the ability to discriminate between a male and estrus female or between a familiar and novel juvenile male rat, suggesting a specific effect of V1aR antagonism on socio-sexual motivation. Preliminary data further indicate that vasopressin-expressing neurons of the pBNST also express mRNA for the V1a receptor. This suggests a mechanism by which vasopressinergic inputs to the pBNST act to modulate the activity of local vasopressin-producing neurons to facilitate socio-sexual motivation. We are currently testing this hypothesis by utilizing a vasopressin promoter-driven virus, chemogenetics, and electron microscopy to determine whether vasopressin-producing neurons in the hypothalamus synapse onto vasopressin-producing neurons in the pBNST and activate local vasopressin receptors.

Disclosures: J.A. Smith: None. **R. Bredewold:** None. **C.J. Reppucci:** None. **A.H. Veenema:** None.

Poster

162. Motivation: Social Communication

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Program#/Poster#: 162.05/PP7

Topic: G.02. Motivation

Title: Neuronal substrates of group decisions and social bias in mice

Authors: *R. BÁEZ-MENDOZA, F. BOUNNI, G. N. FRIEDMAN, Z. M. WILLIAMS
Dept. of Neurosurg., Massachusetts Gen. Hospital-Harvard Med. Sch., Boston, MA

Abstract: Group behavior plays a core role in animal and human behavior. Although group behavior has been explored widely within psychology, ecology, and sociology, the neural mechanisms of this phenomenon remain largely unexplored. Here, we investigated how the activity of single neurons in the rodent medial prefrontal cortex (mPFC) is modulated in response to the behavior of other group members and social biases introduced by their collective decisions. Small groups of wild-type mice foraged together in a T-maze. A pair of mice were trained to consistently explore either the right or left arm of the T-maze, which, in combination with varying the reward location, resulted in positive or negative social biases for the untrained focal mouse. To investigate the neuronal substrates of group decisions as the animals foraged together for food, we recorded from neurons in the mPFC, an area that plays a role in decision-making and social encoding. We also applied deep brain stimulation (DBS) to the mPFC to investigate the causal role that this area plays during group decision making. We found that when the mice foraged together, the behavior of individual animals was significantly influenced by that of the entire group. Importantly, the animals learned to ignore negative social bias. Furthermore, there was no social bias while foraging in an unpredictable environment nor while foraging with inanimate totems. Social influence was reflected by the activity of a specific subset of neurons in the mPFC. Taken together, these neurons encoded the groups' choices in combination with the presence or absence of reward on each arm. Importantly, these neurons reflected little information about the animals' own decisions or reward prediction errors. Applying DBS to the mPFC amplified social bias, particularly negative social bias, suggesting a possible target for DBS placement for treatment of deficits in social interactions. Together, these observations reveal that: (1) individual choices in mice can be influenced by group decisions, (2) these group decisions are reflected in the activity of specific neurons in mPFC, and (3) the mPFC plays a causal role in decision-making during social interactions.

Disclosures: R. Báez-Mendoza: None. **F. Bounni:** None. **G.N. Friedman:** None. **Z.M. Williams:** None.

Poster

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Topic: G.02. Motivation

Title: Single neuron correlates of disrupted social behavior in an ASD mouse model

Authors: G. FRIEDMAN[1], *F. BOUNNI[1], M. JAMALI[1], W. LI[1,2], Z. WILLIAMS[1]
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Abstract: Social dysfunction is among the most prominent features of autism spectrum disorder (ASD) as well as many other developmental and neuropsychiatric conditions. The precise neuronal mechanisms that are disrupted in ASD, however, remain unknown. The goal of this study is to provide a basic cellular-level understanding and treatment model for ASD. To this end, we developed an alternating appetitive/aversive paradigm in which socially-paired mice experienced both acute stress and food reward while we simultaneously recorded neuronal activity from the medial prefrontal cortex. We compared wild-type (WT) to SHANK3 -/+ mice as a model of ASD, to explore the neuronal correlates of socially relevant information and its dysfunction. Individual medial prefrontal neurons in SHANK3 -/+ mice displayed markedly different response profiles compared to that of WT. Specifically, neurons in WT mice demonstrated integration of both the identity of the paired mouse and the valence of the condition, whereas neurons of the SHANK -/+ mice dissociated these two features. Our study reveals some of the basic neuronal coding mechanisms that are disrupted in ASD. In particular, they demonstrate that, at the cellular level, autistic mice separately encode social and conditional stimuli. This neuronal response provides a putative neural mechanism for disrupted capacity for theory of mind, a hallmark characteristic of ASD and suggests a basic model for testing neurobiologically plausible treatments for individuals with autism.

Disclosures: G. Friedman: None. **F. Bounni:** None. **M. Jamali:** None. **W. Li:** None. **Z. Williams:** None.

Poster

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Topic: G.02. Motivation

Support: MEXT/JSPS KAKENHI Grant 16K13274

MEXT/JSPS KAKENHI Grant 15H01771

MEXT/JSPS KAKENHI Grant 17H01753

Title: Shared subjective experience and interpersonal neural synchronization in foreign language active learning classroom: A pilot study

Authors: *T. NOZAWA[1], M. KONDO[2], R. YAMAMOTO[2], H. JEONG[3], S. IKEDA[3], K. SAKAKI[3], Y. ISHIKAWA[2], Y. MIYAKE[1], R. KAWASHIMA[3]

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Abstract: Flow is a highly motivated and affectively positive state where a person is immersed deeply into the activity at hand and feeling enjoyment in it. In a classroom it is the ideal situation that all students keep in the state of flow. However in reality, flow states fluctuate divergently among students, reflecting individual differences in the dynamics of motivation and cognition. To explore the possibility that interpersonal neural synchronization (INS) provides a quantitative measure for the divergence of collective motivational dynamics, we conducted a pilot study and investigated the relationship between the students' INS and the interpersonal similarity of flow state dynamics during the active learning process in the classroom. In two English as foreign language (EFL) classes in a Japanese university, 1st- or 2nd-grade students (27 in a class and 29 in the other) were divided into groups of four or three members, seated at desks facing to each other, and conducted a 60-minute group work. In each of the two classes, two groups consisting of four members were randomly selected, and their medial frontopolar neural activities were simultaneously measured using wireless functional near-infrared spectroscopy (fNIRS) devices. Their group work activities were also video-recorded. Later the participants observed their own activities on the video and retrospectively rated on a seven-level scale their subjective degree of flow state for each period of two-minute segments. For pairs of students whose neural activities were measured in each of the two classes, the similarity of their flow experience dynamics was evaluated by the temporal correlation between their flow ratings. Frontopolar INS of the same student pairs during the group work was evaluated using the wavelet transform coherence. The results of statistical tests on data of all pairs over the two classes showed that (1) the flow dynamics was significantly more similar for the student pairs within the same group compared to the pairs of students assigned to different groups; (2) frontopolar INS in the relatively small time scale overlapping to the "slow3" low-frequency oscillation (0.073-0.198 Hz) was significantly higher for the within-group pairs compared to the across-groups pairs; and (3) the frontopolar INS at the same time scale as above was significantly positively correlated to the similarity of flow dynamics even after adjusting the within-group/across-group effects from the two variables. These suggest that INS indeed provides a quantitative measure for dynamically changing collective motivational states during active learning, with higher INS corresponding to more shared experiences.

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Poster

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Topic: G.02. Motivation

Support: University at Buffalo CTSA Grant

Title: Stimulant drugs increase the reinforcing value of social stimuli and decrease the reinforcing value of sucrose in Fischer-344 rats

Authors: *C. D. MARTIN[1,2], K. CARR[3], L. EPSTEIN[3], L. W. HAWK[1], J. B. RICHARDS[2]
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Abstract: Use of stimulant drugs such as nicotine (NIC) and methylphenidate (MPH) by humans results in lowered bodyweight. Some smokers report maintenance of nicotine use as a weight management strategy. Here, we tested the hypothesis that NIC and MPH would reduce hedonic sucrose consumption by reducing the reinforcing value of sucrose and by increasing the reinforcing value of a social reinforcer used as a non-caloric alternative.
Three groups (saline, *n*=10; NIC, *n*=10; MPH, *n*=10) of adult male Fischer-344 inbred rats were tested for operant snout poking for a sucrose reinforcer with a progressive ratio (PR) schedule of reinforcement. Testing took place across three phases. During the first phase (pre-exposure; PRE) all rats were trained on a PR scale up to PR5 for the sucrose reinforcer. In the second phase (DRUG) the animals were treated with saline (SAL), NIC (0.4 mg/kg, SC), or MPH (2.0 mg/kg, IP) 30 minutes prior to testing, and again run on PR5 for sucrose consumption. In the third phase of testing (SOC) the animals continued to receive drug treatment, and a novel stimulus rat acting as a social reinforcer was made available concurrently with the sucrose in a separate response port, on an independent PR5 schedule of reinforcement. Reinforcing value was defined as the number of responses resulting in the highest within session break point (BP).
The results show that animals treated with SAL maintained a consistent BP for sucrose throughout all phases of testing, indicating no change in reinforcing value. Rats treated with NIC showed no significant change in sucrose BP upon introduction of the drug during the DRUG phase, but exhibited a significant decrease in sucrose BP when the alternative social reinforcer was added during the SOC phase. MPH-treated rats produced a lower BP for sucrose during the DRUG phase relative to the PRE phase, and demonstrated a further reduction in sucrose BP during the SOC phase.
These data indicate that stimulant drugs may decrease consumption of caloric reinforcers by increasing the reinforcing value of alternative, non-caloric reinforcers.

Disclosures: C.D. Martin: None. **K. Carr:** None. **L. Epstein:** None. **L.W. Hawk:** None. **J.B. Richards:** None.

Poster

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Topic: G.02. Motivation

Support: NIH Grant HD075750

Title: Fatherhood is associated with microarchitectural changes in the prairie vole brain: A diffusion-weighted imaging investigation

Authors: *J. R. YEE[1], A. M. PERKEYBILE[2], W. M. KENKEL[2], P. P. KULKARNI[3], C. CARTER[4], C. F. FERRIS[5]
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Abstract: Mammalian fathers in obligate biparental species play a complementary role to mothers, and lacking nursing duties, are well-positioned to aid offspring survival by assessing and handling potential threats. Recent work in our lab demonstrated that fathers display dampened BOLD in the fear circuit in response to predatory life threat, providing a potential neural mechanism to facilitate the approach of fearful stimuli that is oftentimes required for the protection of offspring. But how extensive are these neural changes associated with fatherhood? Are fatherhood-related neural changes limited to functional reactivity, or are they also accompanied by structural changes? In this study, we extend our work on neural changes in fathers by employing diffusion-weighted magnetic resonance imaging (DWI) to characterize grey matter microarchitectural changes in 117 3D-segmented regions throughout the entire vole brain. Prairie voles (*Microtus ochrogaster*) provide an ideal model since fathers within the species play an active and obligate role in offspring care, a trait that is uncommon in rodent species. Preliminary findings demonstrate that the transition to fatherhood is accompanied by both functional and structural changes in the brain. While some brain regions implicated in our analysis have been already shown to be implicated in the transition to paternity (e.g. amygdala, cingulate-retrosplenial cortex, ventral medial hypothalamus), other differences identified by our DWI analysis (e.g. midbrain/pontine reticular regions) have not. Such previously unidentified regions may yet mediate functional changes in basic processes such as attention and arousal that may change with becoming a father. Furthermore, follow-up experiments will employ autoradiography to determine whether the microarchitectural changes revealed by DWI are due to differences in vasopressin receptor expression as others have previously suggested.

Disclosures: **J.R. Yee:** None. **A.M. Perkeybile:** None. **W.M. Kenkel:** None. **P.P. Kulkarni:** A. Employment/Salary (full or part-time):; Ekam Solutions. **C. Carter:** None. **C.F. Ferris:** A. Employment/Salary (full or part-time):; Animal Imaging Research, Ekam Solutions.

Poster

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Program#/Poster#: 162.10/PP12

Topic: G.02. Motivation

Title: EEG changes in pigs during belly rubbing by a human, recorded wirelessly and subdurally

Authors: *J.-L. RAULT[1], L. HEMSWORTH[1], M. LE CHEVOIR[1], S. BAUQUIER[1], A. LAI[2]
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Abstract: Our relationship with domestic animals goes back thousands of years, but the neurobiological response to human-animal interaction remains poorly understood. Wireless recording of brain activity offers new prospects to elucidate neurobiological processes in free-moving animals. We investigated changes in the electroencephalogram (EEG) of 6 pigs during positive human contact, specifically in the form of gentle belly rubbing. The EEG montage consisted of a single-channel recording with 2 subdural electrodes placed under surgery through skull holes, one caudal and medial to the supraorbital foramen and the other lateral and caudal to the fronto-parietal suture to englobe the left cortex, and connected to a wireless EEG transmitting implant placed subdermally in the neck. Tests started 3 days post-surgery, every other day for 5 days. Pigs were moved individually to a familiar test room, given 2-min to habituate, before undergoing a series of 5 (day 1) or 3 (days 3 and 5) 2-min sessions of human presence and contact, alternated with 2-min isolation. From videos, we scored spontaneous belly rubbing behavior applied by one familiar human, which typically elicits a distinct behavioral response characterized by lateral recumbency, limb extension, and often frequent short-lasting grunts and eye closure. As comparisons to belly rubbing bouts, we used: the remaining 2-min human contact sessions when belly rubbing did not occur (these involved human contact or mere presence depending on the pig's voluntary approach); a session of 2-min isolation following the 2nd human contact session in each series; and a 2-min session prior to the test in the home pen without human present as baseline. EEG data were sampled at a 1,000 Hz rate, processed per 1-sec bin using a Fast-Fourier transformation for power spectral analysis and cleaned for artefacts (defined as median frequency 'F50' > 40 Hz), to derive the medians for total EEG power ('PTotal'), 95% spectral edge frequency ('F95') and F50 over 5-sec epochs. Pigs varied in their receptivity to belly rubbing but all displayed it, in 13 of 18 tests and 28 of 66 test sessions, for an average bout duration of 67 ± 6 sec. PTotal was lower during human contact and belly rubbing

compared to baseline ($P<0.01$). F50 was higher during belly rubbing (5.3 ± 0.9 Hz) than other tests and baseline (3.8 ± 0.9 Hz, $P \leq 0.03$). F95 was higher during belly rubbing (45.2 ± 3.2 Hz) than other tests and baseline (40.0 ± 3.2 Hz, $P \leq 0.003$). Hence, belly rubbing reduced total EEG power while modifying the spectral power distribution toward higher frequencies. Defining species-relevant frequency bands of the EEG power spectrum could help determine states of neurobiological activity.

Disclosures: J. Rault: None. **L. Hemsworth:** None. **M. Le Chevoir:** None. **S. Bauquier:** None. **A. Lai:** None.

Poster

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Topic: G.02. Motivation

Support: GUROP

Pioneer Academics PAR3152015-001

Biomedical Graduate Research Organization at Georgetown University

Title: Effect of Shank3 mutations on zebrafish social behavior

Authors: *S. ASDJODI, A. PRASAD, E. GLASGOW, J. KANWAL
Georgetown Univ., Washington, DC

Abstract: Autism spectrum disorder (ASD) impacts millions of individuals each year in the United States alone. Recently, Zebrafish (*Danio rerio)* have become promising models for investigation of the molecular and neurological underpinnings of ASD. Shank3, a scaffolding protein in the dendrites of postsynaptic neurons, has been linked to ASD. Mutations in Shank3 can impair synaptic function and create neurological conditions and symptoms similar to those observed in ASD. We used zebrafish as a model organism to investigate the role of Shank3 in social behavior, a commonly effected behavior in ASD. To confirm a knockout mutation in Shank3, both Shank3a and Shank3b mutant Zebrafish were genotyped using PCR and restriction enzymes. A decision paradigm was used to test social behavior in wildtype EK and mutated zebrafish. Fish were placed in a chamber with the option to swim to a social or non-social zone. The amount of time spent in each zone was used as a marker for preference for social interaction. We found that the overall social affinity of Shank3 transgenic and wildtype zebrafish was did not differ greatly but overtime, after initial exposure to other fish, Shank3 mutants exhibited decreased social affinity as compared to wildtypes. Thus, Shank3 mutants have decreases

sociability but do not differ in social novelty as compared to wildtypes. These results demonstrate the viability of mutated Shank3 zebrafish as models for ASD.

Disclosures: S. Asdjodi: None. **A. Prasad:** None. **E. Glasgow:** None. **J. Kanwal:** None.

Poster

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Topic: G.02. Motivation

Support: NIH Grants

Title: Transcription factor ΔFosB regulates aggressive behavior in male mice in a cell-specific manner

Authors: *H. ALEYASIN[1], M. FLANIGAN[1], S. A. GOLDEN[2], A. TAKAHASHI[3], J. PINA[1], C. MENARD[1], M. L. PFAU[1], G. E. HODES[4], M. HESHMATI[1], E. A. HELLER[5], S. J. RUSSO[1]
[1]Icahn Sch. of Med. Mount Sinai, New York, NY; [2]Natl. Inst. on Drug Abuse, Baltimore, MD; [3]Univ. of Tsukuba, Tsukuba, Japan; [4]Neurosci., Virginia Tech., Blacksburg, VA; [5]Dept. of Systems Pharmacol. and Translational Therapeut., Perelman Sch. of Medicine, Univ. of Pennsyl, Philadelphia, PA

Abstract: Background: A number of studies implicate reward circuitry as an important modulator of aggression. However, little is known about the mechanisms of gene regulation that control such behavior. Here we explore the role of ΔFosB, a transcription factor and master regulator of reward-motivated behaviors in male aggression in mice. **Methods:** Old and sexually experienced male mice physically interact with novel young, sexually naïve C57BL/6 mice in their home cage (R/I test). Their interactions are recorded and scored for aggressive behavior. To modify ΔFosB we inject viral vectors into the ventral striatum. We use conditional place preference (CPP) to assess the motivational component of aggressive behavior.
Results/Conclusion: We demonstrate an association between the level of ΔFosB in the ventral striatum (VSt), and the intensity of aggressive behavior. We show that ΔFosB is specifically increased in D1R expressing MSNs of VSt in aggressor mice. D1 MSN-specific induction of ΔFosB expression reinforces aggressive behavior in mice measured by R/I test. These data strongly support a cell-specific pro-aggressive role of ΔFosB in the VSt. Altogether our findings help understanding the molecular basis for motivational aspects of aggressive behavior in mice.

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Poster

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Topic: G.02. Motivation

Support: ERC starting grant

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Israel Science Foundation

Title: Autism-associated changes in the representation of social information in prefrontal circuits

Authors: *D. R. LEVY, T. TAMIR, M. KAUFMAN, A. WEISSBROD, E. SCHNEIDMAN, O. YIZHAR
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Abstract: Deficits in social behavior are among the primary symptoms of autism spectrum disorder (ASD). Although little is known regarding the circuit alterations that might give rise to this complex phenotype, evidence from both human patients and animal models suggests that dysfunctions of the prefrontal cortex (PFC) might play a dominant role in ASD pathophysiology. However, a major gap still exists in understanding the role of this region in social processing. More specifically, it is unclear how the PFC encodes social information, and how changes in these representations might correlate with impaired behavioral responses. To address these questions, we utilized a custom-built behavioral apparatus and recorded unit activity in the ventromedial PFC of behaving male mice presented with precisely-timed social and non-social odor cues. We found distinct representation for social stimuli in the vmPFC, such that a large proportion of recorded units (40%) responded exclusively to male or female odors over a repertoire of non-social cues. Cue-responsive units also showed greater response magnitude to social odors than to non-social stimuli. Population-level analyses revealed that while male and female odors evoke similar activity patterns in the vmPFC, these representations are notably distinct from those of non-social cues, regardless of odor valence. In Caspr2 knockout mice, a well established genetic model of autism, these patterns were significantly altered, such that vmPFC units showed decreased specificity to social odors as well as blunted stimulus-evoked response dynamics. Interestingly, spontaneous population activity in knockout mice was also distinct from that seen in wild-type littermates and showed higher overall firing rates and increased baseline variability. Taken together, our results identify specific representations for salient social stimuli in the mouse vmPFC and indicate altered processing of social information in a genetic model of autism.

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Poster

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Topic: G.02. Motivation

Support: NIH Grant RO1 AA013983

Title: Escalation of aggressive arousal by alcohol: Dissociation of motivation and behavioral performance by CRF acting on CRF-R1

Authors: H. E. COVINGTON[1], S. TRAN[1], E. NEWMAN[1], W. RENTHAL[3], K. HA[1], L. WALTON[1], J. DEBOLD[1], *K. A. MICZEK[2]
[1]Psychology, [2]Moses Hunt Professor of Psychology, Tufts Univ., Medford, MA; [3]Neurol., Harvard Univ., Boston, MA

Abstract: Activation of the HPA stress axis is shared across all mammalian species for the initiation of motivated behaviors, particularly when fulfilling physiological and psychological *needs*. Here, the motivation to initiate aggressive acts, as well as the execution of aggressive outbursts, were experimentally examined in inbred C57BL/6J mice. Initially, mice were conditioned to respond on a fixed interval ten minute (FI10) schedule with aggression serving as a reward (i.e., the opportunity to fight with a male intruder). The accelerating pattern of responding established by the FI schedule allows for direct measurements of aggressive motivation. Subsequent to the completion of each FI schedule, the stimulus intruder mouse was presented, and aggressive acts in one bout of fighting were quantified. The role of corticotrophin releasing factor receptor 1 (CRF-R1) was then examined on both, measures of aggressive motivation and fighting performance. Tolerance and sensitization became evident with repeated oral administrations of alcohol (1.8g/kg, gavage) with regards to the motivation to engage in aggressive acts. Interestingly, low doses of the selective CRF-R1 antagonist CP 376395 blocked the expression of alcohol-induced sensitization of aggressive motivation, but without influencing fighting performance. Finally, measurements of *crf, crfr1* and *crfr2* mRNA across the VTA, DRN and LH reveal that the emergence of alcohol-induced sensitization of aggressive motivation occurs with a persistent augmentation of CRF tone in distinct extrahypothalamic CRF circuits. In sum, these experiments are aimed at identifying targets for the motivational components of intense aggressive behavior and the neural elements that control reactive “hot” acts of aggression that become sensitized by repeated exposures to alcohol.

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Poster

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Topic: G.02. Motivation

Support: DP1MH103908

HD087795

5R01-DC013826

Title: Identifying a neural gate for courtship vocalizations in the mouse

Authors: ***K. A. TSCHIDA**, V. MICHAEL, K. SAKURAI, R. MOONEY, F. WANG
Duke Univ., Durham, NC

Abstract: Vocalization is an essential medium for communication that depends on neural networks spanning the forebrain and brainstem. How brainstem neurons encode and control vocalizations remains poorly understood, but answering this question is central to cracking the neural code for vocal communication. The periaqueductal gray (PAG) is a highly conserved midbrain structure that is thought to be essential in controlling vocalizations in a wide range of vertebrates. Identifying the cellular basis of this gate has been challenging because the PAG serves many different functions, and vocalization-related PAG neurons are intermingled with PAG neurons that contribute to other behaviors, including freezing responses to predator odors. Understanding how the PAG controls vocalization requires novel methods to permanently tag PAG neurons that are transiently active during vocalization and subsequently manipulate their activity in freely vocalizing animals.
To this end, we used an innovative genetic method (Capturing Activated Neuronal Ensembles; i.e., CANE (Sakurai et al., Neuron, 2016) to permanently tag and thus identify PAG neurons that are transiently active in adult male mice when they produce ultrasonic vocalizations (USVs). Using this method, we labeled PAG-USV neurons with GFP, allowing us to identify these cells and map their axonal projections to various regions, including the lateral parabrachial nucleus and nucleus retroambiguus. We then used CANE to drive the expression of tetanus toxin in PAG-USV neurons, a manipulation that irreversibly blocks neurotransmitter release onto downstream neurons. Unlike control males, males in which PAG-USV neurons were silenced with tetanus toxin did not vocalize to nearby females, even though these muted males exhibited otherwise normal courtship behaviors and still froze in response to predator odors. Notably, we

found that female mice preferred to spend time near vocalizing males rather than males that were rendered mute by tetanus toxin treatment. Finally, we found that either chemogenetic or optogenetic activation of PAG-USV neurons was sufficient to elicit USVs in isolated males, which typically vocalize little or not at all in the absence of either a female mouse or odorants present in female urine. Taken together, these studies identify a population of PAG neurons, the activity of which is necessary and sufficient to produce USVs, while also supporting the idea that male USVs function as a salient courtship signal.

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Poster

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Topic: G.02. Motivation

Support: XDB02030005

Title: Neural activities during sexually dimorphic social behaviors

Authors: *Y.-C. WEI[1], S. WANG[2]
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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: Y. Wei: None. **S. Wang:** None.

Poster

162. Motivation: Social Communication

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Topic: G.02. Motivation

Support: R01-MH058616

R01-MH099085

R01-MH109450

Title: Consequences of prenatal exposure to valproic acid in prairie vole social behaviors

Authors: *L. L. ELVIR[1], F. DUCLOT[1], Z. WANG[2], M. KABBAJ[1]
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Abstract: Previous studies have shown that rats and mice prenatally treated with sodium valproate (valproic acid, VPA) exhibit deficits in social behaviors that resemble some aspects of autism spectrum disorders. Although significant discoveries on the embryopathology of VPA have been proposed, not one study has assessed its effects on social bonding, a complex behavior not exhibited by rats and mice. In this study, we aimed at validating the socially monogamous prairie vole (*Microtus ochrogaster*) model for the study of the effects of prenatal VPA exposure. Male control and VPA-prenatally exposed subjects were assessed on a battery of behavioral tests to evaluate the VPA-induced social deficits and anxiety-like behavior. VPA-pretreated voles engaged in fewer play behaviors, had reduced social interactions with novel conspecifics of the same age, and showed enhanced anxiety-like, compared to controls. We are now in the process of examining how social bonding behaviors, such as partner preference formation and selective aggression, are disrupted in response to prenatal exposure to VPA. Additionally we examined in the prefrontal cortex, mRNA expression of genes that modulate social bonding in prairie voles, such as the oxytocin (*oxtr*) and vasopressin (*avpr1a*) receptors, as well as genes largely implicated in neurodevelopmental disorders and involved in synaptic formation and signaling, such as Shank3, Nlgn3, and MeCP2.

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Poster

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Title: Molecular mechanisms underlying pair bond maintenance in the socially monogamous prairie voles

Authors: *F. DUCLOT[1,2], L. L. ELVIR[1,2], Y. LIU[3,2], Z.-X. WANG[3,2], M. KABBAJ[1,2]
[1]Biomed. Sci., [2]Program in Neurosci., [3]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Social affiliation is a core characteristic of human social behaviors and related impairments are a common feature in a multitude of neuropsychiatric disorders including schizophrenia and autism spectrum disorders. As a result, understanding the neurobiology of social attachment is of critical importance. In this context, the socially monogamous prairie vole (*Microtus ochrogaster*) provides an excellent opportunity to study the molecular mechanisms underlying the formation and maintenance of a pair bond. Indeed, in prairie voles, prolonged cohabitation with an opposite-sex conspecific leads to the development of an enduring social bond reflected at the behavioral level by selective aggression towards an unfamiliar conspecific. At the molecular level, the maintenance of the bond is associated with alterations in the expression of the dopamine D1 receptor and dynorphin levels in the nucleus accumbens (NAc). In this study, we first characterized the nature of neuroadaptations occurring in the NAc of adult prairie voles that cohabitated for 3 weeks with an opposite-sex partner—or a same-sex conspecific as a control—and tested for selective aggression to verify the establishment of the pair bond. Notably, in order to discriminate regulations specific to the maintenance phase of the bond, a third group of animals were cohabitated with an opposite-sex partner for 24 hours only. Furthermore, as we previously uncovered that the initiation of the social bond in prairie voles involved histone acetylation events, we will here investigate the epigenetic regulation of the *Drd1a* gene encoding for the dopamine D1 receptor, through mechanisms including histone and DNA methylation. In addition to further detail the nature and extent of neuroadaptations specifically associated with an enduring pair bond in the socially monogamous prairie voles, these data will provide a novel insight into the epigenetic processes regulating the maintenance of a social bond.

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Poster

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.19/PP21

Topic: G.02. Motivation

Title: Reunion behavior in adult female degus

Authors: N. K. LIDHAR[1], A. THAKUR[1], A.-J. DAVID[1], K. TAKEHARA-NISHIUCHI[2], *N. INSEL[3]
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Dept. of Psychology, Univ. Toronto, Toronto, ON, Canada; [3]Dept. of Psychology, Univ. of Montana, Missoula, MT

Abstract: The drive to interact socially can be general or stimulus-specific. While isolation and other stressors can increase how much an animal engages with others, increased interaction can also arise from a drive to establish or re-establish relationships with a specific individual. And different sources of social motivation may lead to different types of interactions. The present experiments tested how stress, either by social isolation or exposure to unpredictable footshock, impact the duration and pattern of social interactions relative to separation from a specific individual. The experiments were performed in degus, a diurnal rodent from Chile, because of their rich repertoire of social behaviors and their potential as a laboratory model for neuroscience (e.g., Colonnello et al., 2011). Degus were either isolated for varying periods of time (1 min, 45 min, 24 hrs), exposed to a series of footshocks or food reinforcers (45 min), or separated without isolation by housing four to a cage and then splitting cages into two groups (24 hr separation time). Physical and vocal interaction data were subsequently collected during a 20 minute session when animals were reunited with former cagemates or, in a separate 24 hr isolation condition, stranger conspecifics. Data showed that while the amount of physical and vocal interactions increased with increasing isolation time, levels in non-isolated, separated pairs were at least as high as those following 24 hr isolation. Footshock also had no detectable impact on levels of interaction; however, both isolation and footshock stressors did reduce the latency before individuals began interacting, shifting the distribution of interactions over time as though reducing the beta term of a log-logistic curve. Additionally, both physical and vocal interactions were higher between strangers compared with cagemates, with apparent differences in the proportions of vocalization types used. These results demonstrate that novelty or recency of contact between specific individuals is a strong motivator for degu social interactions, consistent with a drive to establish or re-establish social relationships. They furthermore provide a starting point for relating specific behaviors to neural processes supporting social motivation and behavior.

Disclosures: N.K. Lidhar: None. **A. Thakur:** None. **A. David:** None. **K. Takehara-Nishiuchi:** None. **N. Insel:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.20/PP22

Topic: G.02. Motivation

Support: NIH Grant R21MH111104

Title: The role of specific vasopressin cell populations in the regulation of social communication

Authors: *N. RIGNEY[1], G. J. DE VRIES[2], A. PETRULIS[2]
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Abstract: The neuropeptide arginine-vasopressin (AVP) has long been implicated in the regulation of social behavior and communication in diverse taxa but the source of AVP release relevant for behavior has not been precisely determined. Potential sources include hypothalamic cell populations such as the paraventricular (PVN), supraoptic, and suprachiasmatic nuclei as well extrahypothalamic cell groups in the extended amygdala. To address if AVP cells in the PVN are important for male mouse social communication, we targeted this area in AVP-cre positive mice (expressing cre-recombinase under the control of the AVP promoter), or AVP-cre negative littermate controls, with viral-mediated delivery of cre-dependent caspase-9 suicide construct and assessed levels of urine marking (UM), ultrasonic vocalizations (USV), and social investigation of male and female conspecifics. Preliminary results indicate that partial lesions of the PVN AVP cell population increased affiliative USVs and decreased territorial UM levels compared to littermate controls, without altering overall social investigation or interest in opposite-sex individuals. These results suggest that AVP released from PVN normally inhibits courtship or affiliative behavior and possibly stimulates competitive signaling. Additionally, using rabies-virus mediated input tracing, we identified monosynaptic inputs to PVN-AVP cells from the ventromedial hypothalamus, a structure previously implicated in mouse aggressive behavior. This observation suggests a possible neural substrate regulating murine aggression.

Disclosures: **N. Rigney:** None. **G.J. De Vries:** None. **A. Petrulis:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.21/PP23

Topic: G.02. Motivation

Title: Evidence of rejection of a sexually receptive female rat by a group of male rats

Authors: *A. FERREIRA-NUNO[1], A. CRUZ-BENITES[2], A. MORALES-OTAL[2]
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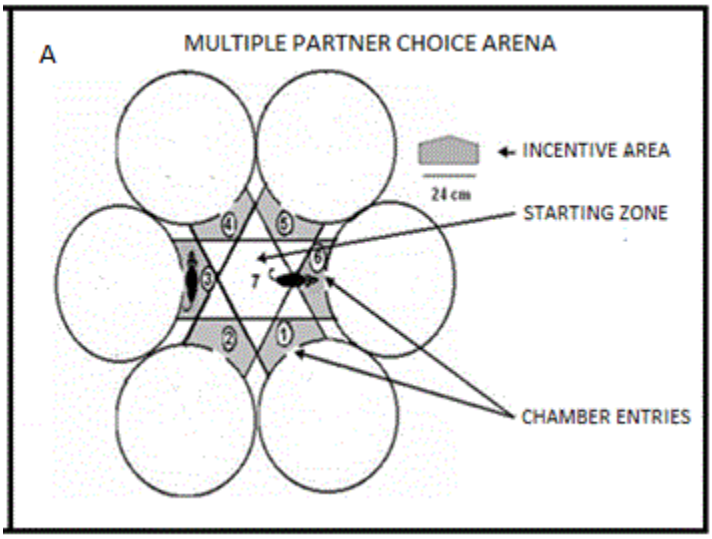
Abstract: Although under a multiple-partner paradigms (MPP) male rat prefers the female visited in first order, it has not been tested whether a group of males may prefer or reject a particular female when they are mated with the same females. With this goal, two groups of sexually expert male rats (n=7, each) were subjected to 3 consecutive tests in a MPP (Fig.A)

made with 6 plexiglass cylinders arranged in a closed circle. In this MPP, an experimental male (ExM), which was placed in the central compartment, was allowed to choose a partner through access doors placed in the base of the cylinders containing the females. First during 5 min the time spent by the ExM in front of 6 dishes containing soiled bedding from 6 receptive females (Lordosis Quotient > 90%) were registered. Each dish was placed behind the door of each cylinder. After this, the females who obtain the higher and the lower scores in the total time spend by the males investigating the soiled bedding were selected for the next trial (2 females in each case). During the 5 min 2nd test, the total time spend by the males of the same group, in front of the soiled bedding from the 4 females selected were scored. Finally in the 3rd test, the soiled bedding dishes were replaced with the respective females and the ExM had the oportunity to mate with the partner chosen. During a 30 min the order and number of visits as well as the number and kind of sexual contacts done by the ExM were registered. These consecutive tests were repeated weekly during 3 times with each group of males, using 4 stimuli females choosen in this way. Although in most of the trials the female of 1st entry was the female preferred, in no case most of the males of a group preferred a particular female. However, in one case, a particular female was rejected, as none of the males visited her first or received from them an ejaculation. Also this receptive female received from males significantly less number of visits and sexual contacts and obtained the lower score in the previous odor preference test. Then a group of male rats can reject a receptive female.



Disclosures: **A. Ferreira-Nuno:** None. **A. Cruz-Benites:** None. **A. Morales-Otal:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.22/PP24

Topic: G.02. Motivation

Title: Neurocomputational substrates of learned and perceived control

Authors: *S. NA[1], J. JUNG[3], V. G. FIORE[3], A. HULA[4], X. GU[2]
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Abstract: Humans are not passive responders to the environment. Instead, we use the impact of our behaviors to exert control over the environment. Here we examined how humans compute learned and perceived control in the brain using functional neuroimaging, computational modeling, and a social exchange paradigm in which participants' behaviors could change the partner's proposed offer in the future. Behaviorally, participants successfully increased the offers they received when they had control and exhibited more "diffused" choices (i.e. choices less coherent with their decision criteria). Neurally, controllability increased the encoding of prediction errors in the ventral striatum and ventromedial prefrontal cortex (vmPFC), and enhanced vmPFC-lateral frontal and vmPFC-insula synchronizations. Having control also decreased the signaling of outcomes in the striatum. Furthermore, activity and connectivity of the striatum, but not vmPFC, distinguished people who perceived high control from those with low perceived control. Taken together, these results suggest that perceived and learned controllability decrease sensitivity to outcome and enhance learning, a process encoded by mesolimbic dopamine regions.

Disclosures: S. Na: None. **J. Jung:** None. **V.G. Fiore:** None. **A. Hula:** None. **X. Gu:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.23/PP25

Topic: G.02. Motivation

Support: Lambda Chi Alpha Fraternity

Title: A noreadrenergic hypothesis of social engagement and exclusion

Authors: *R. W. ROOSEVELT
Psychology, Indiana Univ. Southeast, Louisville, KY

Abstract: Humans are intensely social organisms which depend on maintaining social engagement with others in order to preserve healthy functioning. Consequently, humans are exquisitely sensitive to signs of social rejection. Social exclusion has been intensively studied

experimentally with various neural structures (e.g. amygdala, PFC), endocrine (e.g. cortisol, testosterone, and oxytocin) and genetic contributors (e.g. MAOA, COMT, SERT) having been identified. To date, how these factors interact in social engagement has not been clarified. Here, a noradrengic hypothesis of social exclusion is proposed and results of one prediction of that hypothesis are presented. The locus Coeruleus (LC) is the source of CNS NE and projects widely throughout the CNS to structures implicated in social engagement including those of the limbic system and frontal cortices. The LC produces both tonic output (associated with arousal) and phasic output (associated with stimulus processing). Moreover, the architecture of LC projections are such that LC influences can organize and coordinate activities of structures throughout the CNS. NE is implicated in cortisol regulation and variation in NE metabolism alters availability of NE to act on CNS targets. Additionally, descending LC signals strongly influence heart rate variability and associated social engagement system activities. Thus, level of tonic LC activity should be expected to influence salience of an inclusion/exclusion event and phasic activity should be related to monitoring ongoing relevant stimuli. Cyberball (CB) is a widely employed model of SE, however it only weakly activates the HPA. This weakness is reflected in poor induction of negative affect. We hypothesized that CB paired with cold pressor-induced SNS challenge would induce stronger HPA and affective responses than CB alone. The CP exclusion group exhibited significantly greater HPA response from baseline and the control groups following SE. The CP exclusion group also demonstrated greater increase in negative affect and unprovoked aggression compared to controls. These results support the hypothesis that central noradrenergic system activity organizes and potentiates processing of social exclusion.

Disclosures: R.W. Roosevelt: None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.24/PP26

Topic: G.02. Motivation

Support: NIMH no. MH093412

NSF GRFP

Title: Social affective behaviors activate insular cortex and require PKC

Authors: *M. M. ROGERS[1], J. A. VARELA[2], J. P. CHRISTIANSON[2]
[1]Dept. of Psychology, [2]Psychology, Boston Col., Chestnut Hill, MA

Abstract: Social animals can detect the affective state of others to organize appropriate social behaviors, a phenomenon termed social affect. Here we explore the mechanisms underlying

social affect in a test in which an adult male rat is presented with a pair of unfamiliar male conspecifics, one of which is stressed via 2 footshocks and the other naïve to treatment. Test rats prefer to interact with a stressed juvenile (PN30) conspecific, but will avoid a stressed adult (PN50) conspecific. Fos immunoreactivity indicates that exposure to stressed PN30 versus PN50 conspecifics differentially activates the insular cortex (IC). IC is anatomically positioned to process social affective information and contains a dense distribution of oxytocin receptors (OTR). IC oxytocin (OT) augments intrinsic and synaptic plasticity and is critical to SAP behavior. Here we tested whether the effects of OT, a G_{q11} coupled receptor, are mediated by PKC by applying the PKC antagonist Gö-6893 (200nM) *in vivo* and *in vitro*. Bilateral IC infusion of Gö-6893 abolished social affective behavior and OT failed to alter synaptic or intrinsic excitability in the presence of Gö-6893. These data suggest that OT, vial intracellular PKC signaling is a critical mediator of social affect in the IC.

Disclosures: M.M. Rogers: None. **J.A. Varela:** None. **J.P. Christianson:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.25/PP27

Topic: G.02. Motivation

Support: Brain Canada Grant

Title: Social interaction impairments in female genetic absence epilepsy rats from Strasbourg: Reversal by the T-type calcium channel antagonist Z944

Authors: *W. N. MARKS[1], *W. N. MARKS[1], M. T. HENBID[2], M. J. COLLINS[2], S. M. CAIN[3], T. P. SNUTCH[3], J. G. HOWLAND[1]
[1]Physiol., [2]Univ. of Saskatchewan, Saskatoon, SK, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Childhood absence epilepsy (CAE) is associated with interictal co-morbid symptoms including abnormalities in social behavior. Genetic Absence Epilepsy Rats from Strasbourg (GAERS) is a model of CAE that exhibits physiological and behavioural alterations characteristic of the human disorder. However, it is unknown if GAERS display the social deficits often observed in CAE patients. Social interaction behaviours in rodents are thought to be mediated by neurological circuits densely populated with T-type calcium channels. GAERS contain a missense mutation in the Cav3.2 T-type calcium channel gene. Thus, the objective of this study was to examine the effects of the high affinity T-type calcium channel blocker, Z944, on social interaction behaviors in male and female GAERS relative to non-epileptic control (NEC) animals. Female GAERS showed impairments in a three-chamber sociability task and

open field social interaction task whereas male GAERS performed similarly to NECs. In drug trials, systemic pretreatment with 5 mg/kg of Z944 normalized sociability in the three-chamber sociability task in female GAERS. Reduced dominance behaviours in female GAERS were also increased following Z944 treatment. In contrast, male and female NECs showed impaired sociability following Z944 treatment. Decreased locomotor activity was noted following Z944 treatment in both strains. Overall, the data suggest that T-type calcium channels play a critical role in the regulation of social interaction behaviour in both GAERS and NEC animals. Future research should focus on specific T-type calcium channel subtypes for the treatment of social interaction deficits observed in disorders such as CAE.

Disclosures: W.N. Marks: None. **M.T. Henbid:** None. **M.J. Collins:** None. **S.M. Cain:** None. **T.P. Snutch:** None. **J.G. Howland:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.26/PP28

Topic: G.02. Motivation

Support: NIH Grant R21MH111104

Title: Effects of clozapine N-oxide on social communication in mice expressing inhibitory DREADDs in BNST-MPOA

Authors: *L. KREVITT, D. NGUYEN, A. PETRULIS
Neurosci., Georgia State Univ., Atlanta, GA

Abstract: The neural architecture of social communication is not well described but likely depends on steroid-dependent brain areas within a broader social behavior brain network. One such area, the bed nucleus of the stria terminalis (BNST), has been broadly implicated in social behavior--but little is known about how the BNST affects social communication. We used a chemogenetic approach via viral-mediated Designer Receptors Exclusively Activated by Designer Drugs (DREADD) expression to study the effects of acute BNST inactivation on social communication. Inhibitory DREADDs cause temporary neuronal hyperpolarization upon systemic injection of clozapine N-oxide (CNO), an otherwise inert drug. Adult male mice were injected bilaterally with a viral vector expressing either fluorophore only (control) or inhibitory DREADD expressing virus. Urine marking and ultrasonic vocalizations were measured in the three-chamber sociability apparatus during exposure to a clean arena, an arena containing an adult male, or an arena containing an adult female. Because these behaviors vary widely among individuals, we studied the effects of BNST inactivation using a within-subject design in which all mice were given pre-test CNO (5 mg/kg) and pre-test saline on separate tests. Surprisingly,

this dose of CNO affected urine marking (but not ultrasonic vocalizations) in a manner that was dependent on testing conditions but independent of DREADD expression. In both DREADD mice and control mice, CNO reduced female-directed urine marking and increased male-directed urine marking compared to saline injections. These results indicate that CNO can exert DREADD-independent effects on context-dependent social behaviors. Inclusion of within-subject comparisons, when feasible, may help us better understand the limits, mechanisms, and perhaps even unexpected uses of chemogenetics.

Disclosures: L. Krevitt: None. **D. Nguyen:** None. **A. Petrulis:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.27/PP29

Topic: G.02. Motivation

Support: Pioneer Academics

Title: An extended T-maze for automated learning using social reward in zebrafish

Authors: N. NAJIB[1], S. ASDJODI[2], *J. S. KANWAL[3]
[1]Neurol., [2]Dept. of Biol., [3]Dept. of Neurol., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Growing evidence suggests that zebrafish can play an important role in elucidating the genetic and neural mechanisms underlying multiple neurological disorders, such as Alzheimer's (Bai et al. 2007; Xi et al. 2011), Parkinson's (Makhija and Jagtap 2014) and autism spectrum disorders (Stewart et al., 2014). Shank3 mutants are expected to display behavior symptomatic of schizophrenia (Gauthier et al., 2010) and autism spectrum disorder, but its exact role in zebrafish requires further investigation. Therefore, we designed a behavioral assay to simultaneously explore defects in multiple behavioral characteristics. Our paradigm was devised to test locomotor ability, learning and memory, stereotypic behaviors as well as responsiveness to social novelty and sociability. We used social reward for motivating directional turns in freely swimming zebrafish. Our goal was to minimize handling stress, while allowing animals to continuously learn and behave freely under naturalistic conditions. We designed an extended T-maze that required successive turns by the test subject, placed at a pre-specified location, to visualize and approach conspecifics placed inside a small enclosure within the test tank. Stimulus-directed swimming was used to test two-choice spatial learning and memory driven by opportunity to experience social novelty and sociability. First, environmental exploration was exploited to lead the fish to a glimpse of conspecifics. Second, social motivation was used to allow the fish to make a second turn and approach conspecifics through a narrow passage for pursuing visual social interactions. Finally, preference for a dark environment (safety) was used

to motivate fish to continue swimming, making two more turns before reaching place of entry into the maze. The test subjects presumably retain short-term memory of the social reward as they circumnavigate the maze. Testing with wild type fish demonstrated feasibility of the assay for allowing self-motivated learning and testing in successive trials. On average, three test animals "visited" conspecifics 14 times and circumnavigated the entire maze for >50% of the total 'runs'. In the remaining runs, animals tended to make U-turns, preferring to be with conspecifics rather than enter an environmentally safe zone. All animals preferred to spend the majority of their time interacting visually with conspecifics despite a lack of direct contact. Per an ongoing effort towards a genes-to-circuits-to-cures approach using model organisms, we hope our behavioral assay will allow us to specify behavioral defects in Shank3 mutants.

Disclosures: N. Najib: None. **S. Asdjodi:** None. **J.S. Kanwal:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.28/DP10/QQ1 (Dynamic Poster)

Topic: G.02. Motivation

Title: Probing social motivation heterogeneity in young children

Authors: *B. L. THOMPSON, C. M. HOLLAND, D. A. BARON
Div. of Occup. Sci. and Occup. Therapy, USC, Los Angeles, CA

Abstract: There are vast knowledge gaps in understanding neurobiological mechanisms that contribute to the broad heterogeneity seen in social-affective behavior across human populations. This is particularly true for children with neurodevelopmental disorders whereby neural circuitry involving complex mental functions, such as social-affective processing, is disrupted. This processing, which can influence attention, motivation/reward, and emotional regulation, is a difficult construct to test in young children. This is because determining social-affective state is often dependent on intact language skills. While it is well documented that children with autism spectrum disorder (ASD) show disruptions in social behaviors, the underlying mechanisms driving those disruptions is less understood. Theories range in explanations that these social deficits arise from a lack of motivation for social interaction, to aversion to social interaction. These knowledge gaps in both understanding and measuring social-affective processes currently limits the design of effective and scalable interventions for improving disrupted social behavior. In this study, we have built upon our previously established paradigm of conditioned place preference (CPP) for use in young TD and ASD children, 30-60 months of age, by adapting the task for a social unconditioned stimulus. The paradigm utilized straightforward Pavlovian conditioning methods in a custom-built child friendly arena. During the training trials a novel social experimenter was present in one room and interacted with the child in a prescribed

manner. Typically developing children exhibited a strong conditioned preference for the social paired room, thereby establishing that social stimuli are sufficiently salient and reinforcing for conditioning. In comparison, preliminary data from the ASD group is more heterogeneous, with a range of individual responses indicating lack of reward and aversion to the social stimulus as well as intact preference. The social CPP paradigm provides a continuous measure for describing associative learning, and social behavior phenotypes generating a dynamic range of possible behaviors. With a more comprehensive understanding of mechanisms driving social motivation and their putative neural substrates, this study characterizes the underlying heterogeneity of social-affective behaviors in young children. This allows for a better understanding of the mechanisms driving social motivation, and ultimately will support more precise interventions to target and reduce core social-affective symptoms of ASD.

Disclosures: B.L. Thompson: None. **C.M. Holland:** None. **D.A. Baron:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.29/QQ2

Topic: A.02. Postnatal Neurogenesis

Support: CONACYT 252756

CONACYT 253631

Fronteras 374

UNAM-DGAPA-PAPIIT IN203615

UNAM-DGAPA-PAPIIT IN210215

Instituto Nacional de Perinatología 212250-3230-21216-05-15

Title: The formation of the pair bond reduces the density of newborn cells in the anterior accessory olfactory bulb in Microtus ochrogaster: The monogamous prairie vole

Authors: *G. VALERA-MARIN[1], T. AGUILAR-GARCÍA[1], N. F. DIAZ[2], L. J. YOUNG[3], R. G. PAREDES[1], W. PORTILLO[1]
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Abstract: The formation of a strong pair bond characterizes many human relationships, creates a protective buffer against stress or anxiety and facilitates biparental care of the offspring. Most of

the neurobiology of the formation of pair bond has been studied in monogamous rodents as *Microtus ochrogaster,* the prairie vole, which build a pair bond after 6 hours of cohabitation and sexual contact. In the present experiment, we evaluated if the formation of the pair bond could be related with the newborn cells that reach the olfactory bulb, hypothalamic regions or the amygdala. Pairs of prairie voles were randomly assigned to one of three groups (n=8 pairs on each group: a) Control group, where males and females were isolated; b) Pair bonding group, where males and females were allowed to copulate c) Exposure group, where males and females voles were separated by a wire barrier. The behavioral test lasted 6 h and all the animals were injected with 5´- 2' bromodesoxiuridin (BrdU; 100 mg/ ml) three times with a 2 h interval during the behavioral procedure. All females were ovarectomized two weeks before the experiment and primed 4 days with estradiol-benzoate (10µg/ml). Fifteen days after the behavioral test subjects were perfused and processed for BrdU inmunohistochemistry. Our results show that females that mated for 6 h and formed a pair bond had a lower density of BrdU positive cells in the anterior part of the granular cell layer of the accessory olfactory bulb (AOB) compared with control females (Kruskal Wallis; $H = 7.26$, $p<0.05$). No differences were found in other brain regions like the granular or glomerular cell layer of the main olfactory bulb, the posterior granular cell layer of the AOB, glomerular cell layer of the AOB, anteromedial amygdala, medial preoptic area or ventromedial hypothalamus. In females the AOB is a region involved in recognizing pheromonal cues from males. This decrease after the formation of the pair bond could help optimize the olfactory learning and discrimination of the female vole. Further experiments should evaluate if there is a change in the number of newborn neurons.

Disclosures: G. Valera-Marin: None. **T. Aguilar-García:** None. **N.F. Diaz:** None. **L.J. Young:** None. **R.G. Paredes:** None. **W. Portillo:** None.

Poster

162. Motivation: Social Communication

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 162.30/DP11/QQ3 (Dynamic Poster)

Topic: G.02. Motivation

Support: JSPS KAKENHI 17K07052

Tamura Science Foundation

Title: 3D-Tracker, an open-source 3D video based behavioral analysis system for laboratory animals for neuroscience

Authors: *J. MATSUMOTO[1], H. NISHIMARU[1], Y. TAKAMURA[1], K. MIMURA[2], A. ASABA[3], W. SUZUKI[3], N. ICHINOHE[3], T. MINAMIMOTO[2], T. ONO[1], H. NISHIJO[1]
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Imaging, Natl. Inst. of Radiological Sciences, Natl. Inst. for Quantum and Radiological Sci. and Technol., Chiba-shi, Japan; [3]Dept. of Ultrastructural Res., Natl. Inst. of Neuroscience, Natl. Ctr. of Neurol. and Psychiatry, Kodaira-shi, Japan

Abstract: Three-dimensional video based behavioral analyses greatly contribute to various experiments and analyses, which have been difficult in 2D video-based analyses. However, such potential benefits have largely been unexplored, due to a relatively high cost and technical difficulties to set up and utilize 3D video based systems. To facilitate applications of 3D video analysis, we are going to launch an open-source project for a low-cost (<3,000 dollars) and versatile 3D video analysis system, with rich documentations and an online community that help users (www.3dtracker.org). The project is based on a system developed previously by the authors, which utilizes multiple depth cameras to reconstruct a 3D video and estimate the positions of body parts by fitting skeletal models to the 3D videos. The present system has characteristic features; 1) capability to analyze multiple animal species (rodents and monkeys); 2) robust tracking of overlapped animals (e.g., social interaction); 3) estimation of detailed 3D postures without any markers on the animals; 4) fast pose estimation with an algorithm capable of real-time detection of behaviors. These features allow to combine this system with other techniques such as electrophysiology and optogenetics. We call for contributors (both of users and developers) to improve the software and the documentations. In the poster, we will show the outline of the project and present system, and discuss possible applications and future improvements.

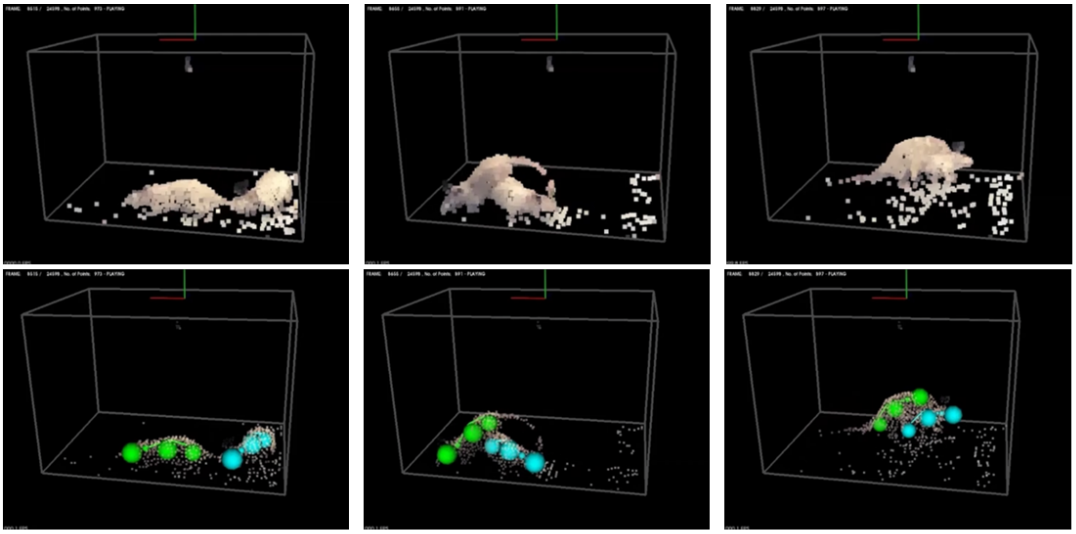

Fig: Examples of reconstructed 3D video frames (top) and estimated positions of skeletal models (bottom).

Check www.3dtracker.org for more examples

Disclosures: **J. Matsumoto:** None. **H. Nishimaru:** None. **Y. Takamura:** None. **K. Mimura:** None. **A. Asaba:** None. **W. Suzuki:** None. **N. Ichinohe:** None. **T. Minamimoto:** None. **T. Ono:** None. **H. Nishijo:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 163.01/QQ4

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA022448;

AFPE Pre-doctoral fellowship

USC School of Pharmacy

Title: Cross-talk between P2X4 and NMDA receptors: Targets for drug development

Authors: L. RODRIGUEZ, A. GUAN, J. LIANG, L. ASATRYAN, *D. L. DAVIES
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Abstract: Purinergic P2X4 receptors (P2X4Rs) are becoming recognized as a target for the development of drugs to prevent and/or treat alcohol use disorder (AUD). This hypothesis is derived from genetic, pharmacological and behavioral evidence reporting an inverse relationship between ethanol (EtOH) intake and P2X4R activity. Less is known regarding how P2X4R activity affects EtOH intake. Of note, another ethanol sensitive, excitatory ionotropic receptor, glutamate (NMDA) receptors, may provide some insight into this question. Both receptors are expressed in areas of the brain associated with ethanol intake and behaviors that are strongly associated with reward, memory and addiction (e.g., ventral tegmental area, nucleus accumbens, hippocampus). For example, previous work links P2X4Rs to voluntary ethanol consumption and NMDA receptors to regulating dopamine neuronal activity, which is an important component of the addiction circuitry. Although much is known regarding the effects of individual receptors on the action of EtOH, little is known regarding receptor interactions and “cross-talk” between receptors and how this affects receptor/ethanol-induced signaling. We hypothesize that receptor cross-talk plays an important role in modulating behavioral and/or sensorimotor functions associated with addiction. In the current study, we tested this hypothesis by investigating interactions between P2X4Rs and NMDARs using two-electrode voltage-clamp electrophysiology and cell-surface trafficking studies in an *X. laevis* oocytes. Baseline studies indicated that P2X4 and NMDA receptors functioned properly (e.g., expected individual channel activity; EC50s, etc) in oocytes that were co-expressing P2X4 and NMDA receptors. However, when applying agonists in a sequential manner, (glutamate followed by ATP, or vice versa) we found that ATP activity via P2X4Rs appeared to suppress NMDAR signaling. On the other hand, NMDA induced signaling did not appear to significantly alter P2X4R activity. Furthermore, we found that when P2X4R stimulation precedes NMDA receptor stimulation, NMDA receptor responses were significantly reduced in a time-dependent manner. Studies are ongoing, but our

preliminary results indicate that P2X4 receptor have the capacity to modulate the response of NMDARs. In that EtOH inhibits both receptors, these findings may begin to shed new information regarding mechanism(s) of action for P2X4Rs and NMDARs in regards to targets for the treatment of AUD.

Disclosures: L. Rodriguez: None. **A. Guan:** None. **J. Liang:** None. **L. Asatryan:** None. **D.L. Davies:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Topic: G.08. Drugs of Abuse and Addiction

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Title: Serotonin 2A receptor activation rescues stress-mediated alterations in ethanol-induced GABA signaling in the ventral tegmental area

Authors: *B. A. KIMMEY, A. OSTROUMOV, J. A. DANI
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Abstract: Hallucinogenic drugs are behaviorally defined by their effects on perception, yet show clinical utility for a growing range of psychiatric illnesses, including alcoholism. Hallucinogens exert their effects, at least in part, through activation of serotonin 2A (5-HT2A) receptors. However, the neuronal mechanisms underlying the therapeutic action of 5-HT2A receptor activation on alcohol abuse remain unclear. We previously found in rats that stress exposure induces an excitatory shift in ventral tegmental area (VTA) GABA signaling thereby increasing alcohol self-administration. The excitatory shift in GABA signaling was mediated by functional downregulation of the neuronal potassium-chloride cotransporter 2 (KCC2) and the resulting impairment of chloride transport in the VTA. Given that 5-HT2A receptor activation has been shown to upregulate KCC2 function, we hypothesized that stress-induced adaptations in GABA transmission, which promote alcohol consumption, could be ameliorated using the selective 5-HT2A receptor agonist (4-Bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2) in a mouse model of stress-induced drinking. Our results revealed that TCB-2 rescues the stress-induced excitatory shift in VTA GABA signaling through restoration of impaired KCC2 function. We found that KCC2-mediated chloride transport was normalized when TCB-2 was bath applied during e*x vivo* electrophysiological recordings. In agreement with this finding, TCB-2 treatment hyperpolarized the depolarizing $GABA_A$ receptor reversal

potential detected after acute stress. Finally, bath application of TCB-2 to slices from stressed animals prevented alterations in VTA neuronal responses to ethanol application. Collectively, these results suggest a mechanism through which engagement of 5-HT2A receptors influences stress-induced neuroadaptations within the VTA and point to the therapeutic potential of 5-HT2A receptor activation in stress-alcohol interactions.

Disclosures: B.A. Kimmey: None. **A. Ostroumov:** None. **J.A. Dani:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Title: Inhibition of the rostromedial tegmental nucleus reverses withdrawal-induced negative affect

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Abstract: Alcohol withdrawal is associated with a hypodopaminergic state and increased negative affect, both of which are thought to play a significant role in the propensity for relapse. The rostromedial tegmental nucleus (RMTg) exerts inhibitory control over midbrain dopamine neurons and activity within this region is associated with the aversive properties of cocaine and alcohol. Together these data suggest that the RMTg plays a role in mediating drug-induced aversive states. To investigate the role of the RMTg in withdrawal and withdrawal-induced negative affect, adult male Long-Evans rats were rendered ethanol dependent using chronic intermittent exposure to ethanol vapor and cFos expression, as well as measures of anxiety-like behavior and anhedonia, were evaluated across the time course of acute withdrawal (0, 6, 12, 24 hr after final ethanol exposure). cFos expression was significantly enhanced in the RMTg during acute withdrawal with peak expression occurring at the 12 hr time point when withdrawal symptom severity is also at its peak ($p \leq 0.01$). A similar pattern of cFos expression was observed

in the lateral habenula - a region that sends prominent glutamatergic projections to the RMTg ($p \leq 0.01$). Likewise, ethanol dependent rats trained to self-administer intra-cranial electrical stimulation exhibited a significant rightward shift in responding across the time course of acute withdrawal with the greatest shift occurring 12 hrs after their final ethanol exposure compared to ethanol-naïve rats ($p \leq 0.05$). This resulted in a significant increase in reward threshold during withdrawal ($p \leq 0.05$). Preliminary data also suggests that inhibition of the RMTg can return reward thresholds to baseline levels. Acute withdrawal was also associated with a significant increase in anxiety-like behavior as measured using open field, elevated plus maze and light-dark box ($p < 0.05$). Inhibition of the RMTg significantly attenuated withdrawal-induced increases in latency to enter the center ($p \leq 0.01$) and time spent in the center ($p < 0.05$) of the open field. Together these data suggest that the RMTg plays an important role in withdrawal-induced negative affect and therefore may be critically involved in the neurobiological mechanisms underlying relapse. Ongoing work is also exploring withdrawal-induced alterations in RMTg neuronal activity using in vivo fiber photometry.

Disclosures: E.J. Glover: None. **E.M. Starr:** None. **Y.S. Chao:** None. **L. Chandler:** None. **T.C. Jhou:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH grant AA020073

Title: Inhibition of intracellular calcium release channels within the rat inferior colliculus suppresses alcohol withdrawal seizures

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Abstract: Altered intracellular Ca^{2+} is known to play an important role in epileptogenesis and the inferior colliculus (IC) is critical in the initiation of acoustically evoked alcohol withdrawal-induced seizures (AWSs). We have obtained evidence that the levels of $[Ca^{2+}]_i$ fluxes were significantly increased in IC neurons 24 hours following alcohol withdrawal, in response to 100 μM ATP (to probe IP3 receptor-sensitive intracellular Ca^{2+} stores) but not to 20 mM caffeine (to probe ryanodine receptor-sensitive intracellular Ca^{2+} stores). The extent to which inhibition of IP3 receptors (IP3Rs) in the IC suppresses AWSs is yet unknown. Here we report on changes of

mRNA encoding for IP3Rs (IP3R-1, IP3R-2, IP3R-3) and ryanodine receptors (RyR-1, RyR-2, RyR-3) in IC neurons following alcohol withdrawal and on the extent to which blockade of IP3Rs or RyRs within the IC suppresses AWSs. Male adult rats were used. For molecular studies, rats were subjected to a 4-day ethanol intoxication paradigm. Control rats were maintained under similar conditions but fed without ethanol. Twenty-four hours after the last dose of ethanol, rats were euthanized and IC tissues were collected for qPCR analysis. For pharmacological studies, infusion cannula was bilaterally implanted in the IC. Following recovery from surgery, rats were subjected to a 4-day ethanol intoxication paradigm and tested for AWS susceptibility 20-24 hours after withdrawal. Rats exhibiting AWSs received infusions of the vehicle, 2-APB (to block IP3Rs; 100 μM/side) or dantrolene (to block RyRs; 20 μM/side), and tested for AWSs. At the end of the experiments, rats were euthanized and brains were collected for histological verification of the microinjection sites. Quantification shows that mRNA expression of IP3R-1, RyR-1 and RyR-2 subtypes were upregulated in IC neurons 3 hours before the onset of AWS susceptibility. The mRNA expression of all IP3R and RyR subtypes was upregulated 24 hours following ethanol withdrawal (when AWS susceptibility peaks). The mRNA expression of all RyR subtypes and IP3-R3 returned to control levels 48 hours following alcohol withdrawal (when AWS susceptibility dissipated), while mRNA expression of IP3R-1 and IP3R-2 subtypes remained upregulated. Seizure testing showed that infusing 2-APB or ryanodine within the IC completely suppressed AWSs by 1 hour and 2 hours post-infusion, respectively. These findings suggest that IP3R-3, RyR-1, and RyR-3 subtypes may provide novel molecular targets for AWSs.

Disclosures: S.J. Cho: None. **J. Newton:** None. **S. Suman:** None. **K. Datta:** None. **P. N'Gouemo:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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NIH/NICHD (DC-IDDRC) 1U54HD090257

Title: Glutamatergic receptor manipulation can attenuate alcohol-induced depressive-like behavior in rats

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Abstract: The high co-morbid occurrence of alcohol use disorder (AUD) and mood dysregulation (e.g. depression) poses an extra medical challenge as each condition may complicate the response or the outcome of the other to a treatment. Indeed, most antidepressants my not be as effective during alcohol use. Conversely, depression that can arise from alcohol withdrawal may strongly contribute to alcohol relapse. Hence, novel therapeutics in such co-morbid conditions are urgently needed. Recent findings suggest that glutamatergic manipulation maybe of significant potential in this regard. Here, we evaluated the effects of chronic administration of sub-anesthetic doses of ketamine, an NMDA receptor antagonist, AMPA, as well as NBQX [2,3-dihydroxy-6-nitro-7-sulfamoylbenzo (f) quinoxaline], an AMPA/kainate receptor antagonist on depressive-like behaviors following withdrawal from chronic intermittent exposure to alcohol vapor. Adult male Wistar rats were exposed to ethanol via inhalation chambers daily (3 h/day) for 7 days, such that a blood alcohol concentration of approximately 150 mg% was achieved during each exposure. This was followed daily by intraperitoneal (IP) injections of: ketamine (2.5mg/kg), NBQX (5mg/kg), alone or in combination with ketamine, as well as AMPA (1 mg/kg). Approximately 18 h after drug treatment, 5 min open field locomotor activity (OFLA) followed immediately by 5 min forced swim test (FST) was performed. Alcohol withdrawal resulted in an increase in OFLA, but a decrease in swimming in FST, suggesting induction of helplessness in these animals. Ketamine had no effect on OFLA following alcohol withdrawal, but normalized the swimming score in the FST. NBQX attenuated alcohol-withdrawal induced increases in OFLA and like ketamine, normalized the swimming score in FST. The combination of the two drugs, however, not only did not result in any additive effect, but actually had no significant effect on either OFLA or swimming score in FST. AMPA treatment also was without any effect. These results suggest that either NMDA or AMPA/kainate receptor antagonists may normalize alcohol-withdrawal induced depressive-like behavior and hence may be of therapeutic potential in AUD. Supported by: NIH/NIAAA R03AA022479 and NIH/NICHD (DC-IDDRC) 1U54HD090257

Disclosures: B. Getachew: None. **Y. Tizabi:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Topic: G.08. Drugs of Abuse and Addiction

Title: A_{2A} receptor regulates ethanol-induced impulsivity in mice

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Abstract: Alcohol use disorder (AUD) is a major global issue for disease and premature mortality. There has been a strong correlation of highly impulsive individuals developing AUD. Thus, impulsivity can be described as a major risk factor for alcohol use disorder. Additionally, alcohol increases the propensity for impulsive behavior, which leads to frequent binge drinking, which could further develop into compulsive drinking, the disease state of AUD where individuals may suffer from withdrawal symptoms. Though there has been vast research of the impact of ethanol in toxicity and increased consumption, the mechanistic role of ethanol in increasing impulsivity has not been thoroughly explored. Here, we designed a binge drinking paradigm using the 5-choice serial reaction time task (5-CSRTT) and ethanol vapor treatments that is similar to human consumption. Animals were trained in the 5-CSRTT while receiving ethanol vapor treatment every three days for four hours sessions. At the end of each week of training, the mice were tested in a “challenge” day in which the inter-trial interval (ITI) was randomized to test for impulse control. Over five weeks, mice that received ethanol vapor treatments displayed excessive premature responses during the challenge tests. Additionally, premature responses became more distinct during the training sessions, where the ITI was held constant, in ethanol treated mice. Next, we seek to understand a mechanism specific to this ethanol-induced impulsivity. Previously our lab found that the A_{2A} receptor antagonism can increase ethanol consumption in mice. Interestingly, the A_{2A} receptor is primarily expressed in striatopallidal neurons and may play an important role in inhibitory control of the indirect pathway of cortico-striato-thalamic pathway. Thus, the A_{2A} receptor is a critical target for determining the development of ethanol-induced impulsivity and must be explored.

Disclosures: **P.A. Starski:** None. **L. Peyton:** None. **A. Oliveros:** None. **D. Choi:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant P50AA017823

Title: Intracerebroventricular administration of interleukin-6 reduces behavioral sensitivity to ethanol exposure in adult male sprague dawley rats

Authors: *T. BARNEY[1], A. GANO[2], A. S. VORE[3], T. DEAK[4]
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Abstract: Binge ethanol exposure produces highly reproducible alterations in neuroimmune gene expression, including increased expression of Interleukin-6 (IL-6) and IκBα, during acute intoxication. These effects are widespread in the central nervous system and are particularly robust in limbic structures such as the hippocampus, paraventricular nucleus of the hypothalamus (PVN), and the amygdala. However, the functional impact of ethanol-dependent IL-6 expression remains unclear. As such, the present study tested the impact of exogenous IL-6 on two common tests of ethanol sensitivity: Loss of Righting Reflex (LORR) and locomotor activity during alcohol withdrawal. To do this, adult male Sprague-Dawley rats (n=50) were stereotaxically implanted with guide cannula targeting the 3rd ventricle and given 7-10 days to recover. Afterwards, rats were injected with 0, 100, or 200 ng of recombinant rat IL-6 delivered in a volume of 2.6 µl icv. Following IL-6 infusion, rats were returned to their home cage for 30 min and then injected intraperitoneally with 4.0 g/kg ethanol (20% solution in physiological saline). A separate group of unoperated rats were included and tested to control for the possible influence of prior cranial surgery on LORR and hypoactivity responses produced by ethanol. . After injection of ethanol, rats were placed in a clean cage and the latency to lose righting reflex and total sleep time were measured. Upon awakening, a blood sample was collected for the assessment of Blood Ethanol Concentrations (BECs) and corticosterone as a secondary index of ethanol sensitivity. Twenty-four hours later, locomotor activity in a novel context was assessed using an automated system (VersaMax) for a period of 30 min. Interestingly, the effect of exogenous IL-6 was dose-dependent, with 100 ng IL-6 significantly reducing sleep time, whereas the effect of the 200 ng dose trended (non-significantly) in the same direction. No significant effects of IL-6 were observed on latency to sleep or BECs. These findings suggest that IL-6 decreases behavioral sensitivity of rats to binge-like doses of ethanol, and are the first indication of a functional role for ethanol-associated changes in IL-6.
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Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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VA Medical Research

Title: Effect of oxytocin on stress-induced reinstatement of alcohol-seeking behavior in male and female mice

Authors: *C. KING[1], H. C. BECKER[2]
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Abstract: Alcoholism is a chronic relapsing disease characterized by periods of abstinence followed by return to heavy use. While many factors contribute to increase relapse vulnerability, stress is considered to play a prominent role in triggering relapse. A growing body of literature suggests that the oxytocin (OT) system plays a role in a number of stress-related psychiatric disorders including alcohol addiction. Work from our lab has demonstrated that systemic administration of OT reduced binge-like alcohol drinking and operant oral self-administration in male C57BL/6J mice. The present study was designed to extend these findings by examining the effects of OT treatment on alcohol relapse-like behavior. Further, there is evidence to suggest that females may be more responsive to stress and are at greater risk for return to heavy drinking following abstinence. Thus, the present study will also aim to investigate potential sex differences in the ability of stress to trigger alcohol relapse-like behavior as well as the ability of OT to attenuate this effect. Adult male & female mice (n=12/group) will be trained to acquire stable rates of lever responding under a fixed-ratio (FR)-4 schedule for 12% ethanol in daily 20 min sessions. Once lever responding and alcohol intake have stabilized (<15% variability over 3 consecutive days) mice will enter into the extinction phase of the study (responding yields no alcohol delivery) for 14 days before reinstatement testing. All mice will undergo stress-induced reinstatement testing using predator odor (2,3,5-Trimethyl-3-thiazoline; TMT). For reinstatement, mice will be exposed to TMT for 15 minutes and immediately placed into operant self-administration chambers to examine alcohol-seeking behavior under extinction conditions. At 30 min prior to the reinstatement test session (15 min prior to TMT exposure), separate groups of mice will be injected (ip.) with vehicle (saline) or OT (0.1, 0.5, 1 mg/kg). We hypothesize that (a) systemic OT administration will attenuate stress (TMT)-induced reinstatement of alcohol seeking behavior in a dose-related manner in male and female mice; (b) females will exhibit greater stress-induced reinstatement of alcohol responding compared to males; and (c) female mice will show a greater response to OT treatment compared to males (leftward shift in dose-response function). Supported by NIAAA grants P50 AA10761, U01 AA014095,U24 AA020929, T32 AA007474 & VA Medical Research

Disclosures: C. King: None. **H.C. Becker:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Support: NIH Grant RO1AA021262

Title: Effect of oral and intraperitoneal administration of pro-dopamine regulator on binge drinking in rats

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Abstract: Binge drinking (BD) is a common pattern of drinking whereby significant alcohol is consumed within a 2 hour period, sufficient to raise blood alcohol concentration to 0.08 g/dL. We hypothesize that BD and abuse of other drugs may be co-morbid with more generalized Reward Deficiency Syndrome (RDS). Mechanistically, RDS is characterized by a reduction in dopamine (DA) signaling within the reward pathway. This type of DA dysfunction is classically associated with increased drug seeking behavior which is also a defining characteristic of RDS. Therefore, it is postulated here, that increasing dopamine availability and thus restoring DA homeostasis in the mesocorticolimbic system could reduce the cravings and motivation to seek and consume ethanol. Recently, among the natural methods used to boost DA levels in brain (such as exercise, meditation and natural products), Neuroadaptagen Amino Acid Therapy has gained momentum. In this study, we used Neuroadaptagen KB220Z/SynaptaGenX (SGX), a nutraceutical product designed to enhance DA homeostasis and to supply the brain with molecular precursors of reward pathway molecules that augment DA signaling. SGX has been tested in many clinical trials for patients with RDS. However, no pre-clinical study is available to elucidate the effects of SGX specifically on ethanol drinking or corticolimbic brain chemistry. Therefore, in this study, using genetically alcohol-preferring (P) adult male (n=6) and female (n=6) rats, we examined the effect of oral gavage (P.O.) and intraperitoneal (I.P.) administration of an animal equivalent dose of SGX (300 mg/kg) on ethanol BD in an operant conditioning chamber. We also investigated potential sex
differences in the effects of SGX. Our data suggests that I.P., but not P.O. administration of SGX led to an immediate marked 52.0 $\pm$ 8.0 % and 65.0 $\pm$ 16.3 % decrease ($p<0.05$) in ethanol consumption by both male and female P rats, respectively. By contrast, significant reduction in ethanol intake was achieved only after 4 days of daily oral administration in P males ($p<0.05$) but not in females, indicating less rapid metabolism by P.O. Furthermore, with I.P., there was an

immediate respective 56.0 ± 8.1 % and 81.4 ± 10.5 % reduction in lever pressing in male and female P rats ($p<0.01$), a measure of motivation to drink ethanol. However, P.O. administration of SGX over 4 days resulted in a modest insignificant 15% reduction ($p>0.05$) in lever pressing by both sexes. Overall, this data suggests that SGX affects drinking behavior in P rats, and I.P. administration is more effective in reducing craving and motivation to drink than oral administration, possibly due to a slower absorption process.

Disclosures: **N. Solanki:** None. **P. Darius:** None. **K. Blum:** None. **M.C. Gondre-Lewis:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Title: Neurotensin in the posterior paraventricular thalamus controls excessive ethanol intake

Authors: *S. PANDEY[1], P. BADVE[1], S. F. LEIBOWITZ[2], J. R. BARSON[1]
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Abstract: Individual differences in vulnerability to alcohol abuse are likely determined by differences in neurochemical profiles in distinct brain regions. We have previously demonstrated in the paraventricular nucleus of thalamus (PVT) that neuropeptide injections can promote pharmacologically relevant ethanol intake in rats. In the present study, we investigated if endogenous neuropeptides within the PVT determine individual differences in levels of ethanol intake. In two groups of adult, male Long-Evans rats (N = 23, N = 20), we found that hind-limb rearing (vertical time) in a novel activity chamber significantly predicts the level of 20% ethanol intake in an intermittent access paradigm. Thus, in a new group of ethanol naïve rats (N = 24), using tertile split with this behavioral measure, we sub-grouped individuals as 'prone' or 'non-prone' to excessive ethanol intake and measured their endogenous neuropeptide mRNA levels within the PVT subregions using quantitative PCR (n = 8/group). We found that prone rats have significantly lower expression of neurotensin (NTS) mRNA in the posterior (p) PVT, but not the anterior (a) PVT. Similarly, in a different group (N = 24), we demonstrated with immunohistochemistry that prone rats also have significantly lower peptide levels of NTS in the pPVT (n = 8/group), suggesting that NTS may act to suppress excessive ethanol drinking. To test

this, we injected NTS (0.12 or 1.2 nmol in 0.3 µl) or saline in ethanol-drinking rats and found that NTS in the pPVT (n = 10), but not aPVT (n = 9), significantly lowered ethanol intake in the first half hour of daily access, when drinking is normally highest. Finally, to see if there is a direct relationship between NTS and rearing behavior that predicts ethanol intake, we injected NTS (1.2 nmol in 0.3 µl, n = 8) or saline (n = 7) in the pPVT and found that NTS reduced vertical but not horizontal locomotor activity. These findings indicate that NTS acts in the pPVT to curb excessive ethanol drinking and suggest that a deficit in endogenous NTS places individuals at high risk for alcohol abuse. Furthermore, the direct link between NTS in the pPVT and rearing, which is indicative of sensation seeking and exploration, suggests that NTS may control ethanol drinking by influencing these traits.

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Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Topic: G.08. Drugs of Abuse and Addiction

Title: Inhibition of phosphodiesterase 2 decreases ethanol intake in mice

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Abstract: Alcoholism, one of the most damaging psychiatric disorders, is caused by excessive alcohol drinking. Reducing alcohol consumption is the major approach to treatment of alcoholism; however, there are no ideal treatments to date. Both cyclic AMP (cAMP) and cyclic GMP (cGMP) signaling pathways are importantly involved in the regulation of ethanol drinking behavior. Our previous studies have demonstrated that inhibition of phosphodiesterase-4 (PDE4), an enzyme that specifically catalyzes the hydrolysis of cAMP, reduces alcohol drinking and seeking behaviors. Thus, it was of particular interest to know if PDE2, an important family of PDEs hydrolyzing both cAMP and cGMP, contributed to the regulation of ethanol consumption. Using ethanol two-bottle choice and drinking-in-dark (DID) tests, we examined the effect of Bay 60-7550, a potent PDE2 inhibitor, on ethanol drinking and preference in C57BL/6J mice. It was found that, treatment with Bay 60-7550 (1 and 3 mg/kg) or rolipram (0.5 mg/kg), a PDE4 inhibitor that has been proven effective, decreased ethanol (7%, 9%, or 12%; v/v) intake and preference by up to 50% of the vehicle control in the two-bottle choice test. In contrast, the treatment did not affect total fluid intake, or intake of sucrose or quinine. In addition, similar to rolipram, Bay 60-7550 decreased ethanol (20%, v/v) intake without affecting water intake in DID. Further, Bay 60-7550 did not affect ethanol-induced sedation, ethanol elimination, or

locomotor activity. These results suggest that PDE2 inhibitors can be used for treatment of alcoholism. PDE2 appears to be a novel target for drugs that reduce ethanol drinking.

Disclosures: Y. Xu: None. **J.M. O'Donnell:** None. **H. Zhang:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

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Title: CRISPR-Cas9 editing of hypocretin (orexin) receptor genes in cell type-specific extended amygdala neurons modulating alcohol drinking and withdrawal-associated behavior

Authors: *L. DE LECEA, W. J. GIARDINO, H. YAMAGUCHI
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Abstract: Lateral hypothalamus (LH) neurons containing the neuropeptide hypocretin (Hcrt; orexin) are critical for maintaining wakefulness and promoting behavioral arousal. LH-Hcrt neurons project widely throughout the brain, acting via two G-protein-coupled receptors (HcrtR1, R2). In addition to reward-related aspects of Hcrt signaling, LH-Hcrt neurons are activated by stressors, and HcrtR antagonists alleviate anxiety-like behavior during withdrawal from chronic nicotine and morphine exposure. Such negative emotional states linked to long-term drug effects are hypothesized to arise from reciprocal connections between LH-Hcrt neurons and cellular populations throughout the limbic circuitry, including extended amygdala neurons of the bed nuclei of stria terminalis (BNST). To investigate cell type-specific BNST-HcrtR signaling, we used a Cre-inducible CRISPR-Cas9 gene editing system in adult mice to specifically target and disrupt HcrtR genes in molecularly-defined neuronal subpopulations. From *in vitro* screening, we selected two single-guide (sg) RNAs targeted to each HcrtR gene (sg-*hcrtr1, r2*). These sequences (and control sgRNA; sg-*ctl*) were cloned into plasmids for production of adeno-associated viruses (AAVs; DJ serotype) containing a Cre-inducible mCherry tag. Cre-inducible Cas9 mice were crossed with knock-in mouse lines expressing Cre recombinase under control of genetic promoters marking BNST subpopulations, including vesicular GABA transporter (*Vgat*), corticotropin-releasing factor (*Crf*), and cholecystokinin (*Cck*). For all studies, we used double-heterozygous $Cre^{+/-}Cas9^{+/-}$ adult male mice. We detected strong HcrtR1 immunoreactivity in *Vgat*-BNST neurons (including *Crf*-BNST neurons, which

comprise a subset of *Vgat*-BNST neurons), and identified a ~70% reduction in HcrtR1 expression in *Crf*-BNST neurons following intra-BNST sg-*hcrtr1* infusion. To test HcrtR disruption in an established mouse model of long-term binge alcohol drinking, we infused AAVs into BNST following three weeks of baseline drinking in the standard intermittent access paradigm, and measured drinking for five weeks following recovery from surgery. Relative to *Crf*-Cas9 sg-ctl mice, *Crf*-Cas9 sg-*hcrtr2* mice showed no differences, whereas *Crf*-Cas9 sg-*hcrtr1* mice displayed significantly reduced alcohol intake and preference. These results highlight an essential role for *Crf*-BNST HcrtR1 signaling in chronic excessive alcohol drinking, independent from traditional limitations of pharmacology and developmentally-sensitive genetic manipulations.

Disclosures: L. de Lecea: None. **W.J. Giardino:** None. **H. Yamaguchi:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 163.13/QQ16

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant AA022048

NIH Grant AA013573

NIH Grant AA015148

Title: The medial prefrontal cortex neuropeptide y (npy) system modulates binge-like ethanol intake

Authors: *S. L. ROBINSON[1], T. E. THIELE[2]
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Abstract: Neuropeptide Y (NPY) is a 36-amino acid poly-peptide widely expressed throughout the brain. Multiple lines of evidence support a role of alterations in the expression and function of the NPY system as an underlying factor in alcohol dependence and in relapse to alcohol seeking/consumption during withdrawal. Further, the NPY system is known to modulate binge-like alcohol consumption in non-dependent animals thought to precede dependence. This system is thus poised to significantly contribute to each stage of alcohol dependence from initiation to withdrawal. The medial prefrontal cortex (mPFC) plays an important role in drug and alcohol-dependence. Importantly, NPY signaling within the mPFC modulates behaviors known to influence drug seeking and intake, such as stress-responsiveness. However, the role of the mPFC NPY system in binge-drinking behavior remains essentially unexplored. Within this work we

evaluated the role of mPFC NPY activity in binge-like alcohol consumption in non-dependent animals through use of the “drinking in the dark” (DID) model. The role of the NPY receptor 1 (NPY1R) in the mPFC were specifically evaluated. In experiment 1, the mPFC of singly housed C57BL/6J male and female mice (Jackson Lab, Bar Harbor, Maine) were bilaterally cannulated. After recovery, mice underwent DID procedures with alcohol or sucrose drinking. Three hours following lights off on day 1-3 of each week water bottles were removed and mice exposed to sipper tubes containing a 20% ethanol or 3% sucrose solution for a 2 hr period. On day 4 ~30 minutes prior to DID session start animals received a microinjection of either a vehicle or a NPY1R agonist using a Latin Square design. Activating mPFC NPY1R significantly reduced alcohol consumption. In a second experiment, inhibitory (Gi-coupled) designer receptors exclusively activated by designer drug (DREADD) or a control virus was injected into the mPFC of NPY1R-cre male and female mice. Animals underwent two cycles of DID identical to that above, save they received an I.P. injection of vehicle or the designer drug CNO ~30 minutes prior to ethanol access on D4. Activation of Gi DREADDs by CNO, but not vehicle injection or CNO injection into CON virus animals, significantly reduced ethanol intake. These results suggest mPFC NPY system modulates ethanol consumption and is of interest in determining the neural underpinnings of alcohol dependence and development of future pharmacotherapies. This work was supported by NIH grants AA022048, AA013573, & AA015148.

Disclosures: S.L. Robinson: None. **T.E. Thiele:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 163.14/QQ17

Topic: G.08. Drugs of Abuse and Addiction

Title: Tdcs for the treatment of alcohol cravings among alcohol abusers

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Abstract: *Background:* Craving is implicated the maintenance of alcohol abuse and dependence as well as relapse during attempts at recovery. A 2008 investigation by Boggio et al. (*Drug & Alcohol Dependence, 92,* 55-60) demonstrated that transcranial direct current stimulation (tDCS) applied over dorsolateral prefrontal cortex (DLPFC) was effective in reducing craving among individuals with alcohol dependence. The present study continued to explore the potential of tDCS to manipulate craving in the context of alcohol use and abuse.
Methods: The study design was a randomized, controlled crossover experiment utilizing repeated measures. Eleven adult participants completed assessments of alcohol abuse severity [Alcohol

Use Disorders Identification Test (AUDIT)] as well as pre- and post-stimulation assessments of alcohol craving [Alcohol Urge Questionnaire (AUQ)] and mood [Quick Mood Scale (QMS)]. Subjects received active and sham stimulation delivered in two separate experimental sessions spaced 3 to 7 days apart. During active stimulation, 2mA was applied for 20 minutes through an anodal electrode placed over the left DLPFC and a cathodal electrode placed over the right DLPFC. Sham stimulation entailed applying 2mA of stimulation for only the first 15 seconds of the session.
Results: Active stimulation produced a significant reduction in craving as measured by change in AUQ scores ($p = .03$), whereas sham did not ($p = .42$). A multilevel model for repeated measures demonstrated that, controlling for alcohol abuse severity (as measured by AUDIT scores), active stimulation produced a greater reduction in craving than did sham stimulation ($p = .03$). In addition, higher AUDIT scores were associated with a greater reduction in craving ($p < .001$), and this effect did not differ between the active and sham conditions. Overall, regardless of whether participants scored high or low on alcohol abuse severity, providing them with active stimulation led to greater reductions in craving relative to sham stimulation. There were no significant changes in mood as measured by the QMS for either condition.
Conclusions: Our results lend further support for the potential of tDCS to modulate craving in individuals with alcohol use disorders who experience frequent or intense cravings. These results motivate additional studies on the utility of tDCS for alcohol abuse in clinical treatment settings. Future research utilizing larger sample sizes and targeting participants who meet the diagnostic criteria for alcohol abuse or dependence is recommended.

Disclosures: D. Rudder: None. **P. Coulombe:** A. Employment/Salary (full or part-time):; University of New Mexico. **C. Tesche:** A. Employment/Salary (full or part-time):; University of New Mexico.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 163.15/QQ18

Topic: G.08. Drugs of Abuse and Addiction

Support: ICM P09-015-F

Puelma Foundation

Title: Vagotomization disrupts Insular reward anticipation procesing

Authors: *S. VICENCIO[1], M. AGUILAR-RIVERA[2], P. E. MALDONADO[3]
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Abstract: Drug addiction is a chronic, relapsing disease which represents a huge burden on our society and that still lacks effective treatments. Drug dependent individuals present altered internal body states (such as visceral sensations and vasomotor activity) that can lead to the increase of the drug's motivational effects thus raising the risk of drug use. The interoceptive system with the insular cortex (IC) as its higher portion, appear as a key element in the representation of the homeostatic afferent signals that drive drug-seeking behaviors. However, the influence that these afferent signals have over the IC function is not yet completely understood. In this regard, we explored how the disruption of visceral pathways could affect the IC activity and the drug motivational effects by resecting the left cervical vagus nerve of alcohol preferring wistar rats. We used an operant conditioning task that allowed us to perform single unit recordings at the IC while the animals were expecting to receive a reward consisting of a 10% alcohol solution. Our results show that in sham animals the IC neurons increased their firing rate when rats were awaiting to receive ethanol and decreased their firing rate while consuming the reward. On the other hand, the IC from the vagotomized animal did not change its firing rate neither in the anticipatory nor the consummatory phase of the task. These results suggest that the disruption of peripheral afferents of the interoceptive system change the way the IC is representing the internal body states and, that this change can reduce the motivation for the drug which affects the decision-making process that underlies alcohol seeking.

Disclosures: S. Vicencio: None. **M. Aguilar-Rivera:** None. **P.E. Maldonado:** None.

Poster

163. Treatment Mechanisms for Alcohol Use Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 163.16/QQ19

Topic: G.08. Drugs of Abuse and Addiction

Title: Preclinical evaluation of the kappa-opioid receptor antagonist CERC-501 as a potential candidate therapeutic for alcohol dependence

Authors: *E. DOMI[1], E. BARBIER[1], E. AUGIER[1], G. AUGIER[1], D. GEHLERT[2], R. BARCHIESI[1], A. THORSELL[1], M. HEILIG[1]
[1]Dept. of Clin. and Exptl. Medicine,, Linkoping, Sweden; [2]Matrix Pharma Consulting, Boulder, CO, United States Cerecor, Baltimore, MD, United States, Baltimore, MD

Abstract: Considerable evidence suggests that kappa opioid receptors (KORs) and their endogenous ligand dynorphin (DYN), play an important role in stress responses, anxiety, depression and addiction related behaviors. In rats, the (DYN)/(KOR) system undergoes ethanol-induced neuroadaptations and results in excessive operant self-administration as well as negative affective-like states.Preclinical data show that JDTic, a selective KOR antagonist reduced alcohol drinking and cue induced reinstatement. More recently, CERC-501 (previously

LY2456302), [(S)-3-fluoro-4-(4-((2-(3, 5-dimethylphenyl) pyrrolidin-1 yl) methyl) phenyl)benzamide]), a highly selective and centrally penetrant canonical KOR antagonist has been shown to reduce EtOH self-administration in alcohol preferring rats both after acute and chronic administration at doses that selectively occupied KORs in vivo. In the present study, we evaluated CERC-501 (0, 3, 10 mg/kg) in anxiety-like behaviors during acute alcohol withdrawal, self-administration and reinstatement of alcohol seeking in Wistar rats. We found that acute oral administration of CERC-501 at the higher dose (10 mg/kg) decreased anxiety-like behavior during acute alcohol withdrawal and decreased operant self-administration as well as motivation for alcohol consumption. Moreover, CERC-501 prevented stress-induced reinstatement, but had no effect on cue-induced alcohol seeking. We also showed that the effects of CERC 501 are specific to alcohol, as there was no effect of CERC 501 on saccharin self- administration. In contrast to JDTic, CERC does not show long-lasting effect, making it a promising therapeutic target for clinical development for the treatment of alcoholism.

Disclosures: E. Domi: None. **E. Barbier:** None. **E. Augier:** None. **G. Augier:** None. **D. Gehlert:** None. **R. Barchiesi:** None. **A. Thorsell:** None. **M. Heilig:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.01/QQ20

Topic: H.01. Animal Cognition and Behavior

Support: NIMH BRAINS grant MH104255

Title: Impaired OCD-relevant cognitive flexibility and altered cortico-striatal activity in SAPAP3 knockout mice

Authors: *E. E. MANNING, M. M. TORREGROSSA, S. E. AHMARI
Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: *Background*: Functional imaging has strongly implicated cortico-striatal dysfunction in the pathophysiology of obsessive compulsive disorder (OCD). However, the mechanisms by which this dysfunction gives rise to OCD symptoms are unclear, with hyperactivity typically observed at baseline and during symptom provocation, and hypoactivity typically observed during cognitive testing. Studies in preclinical rodent models provide a unique opportunity to investigate this discrepancy. To date, transgenic mouse models have provided substantial insight about striatal dysfunction underlying OCD-relevant compulsive grooming. In contrast, there are no studies to date examining the neural basis of cognitive changes in OCD-relevant mouse models.
Methods: SAPAP3 knockout mice (KOs), a leading transgenic OCD model, were tested in an

operant reversal learning paradigm to assess cognitive flexibility. Cortico-striatal activation during reversal learning was assessed via quantitative cFos expression. Analyses included cross-region correlation to infer network functional connectivity, and comparison of neural activity to reversal behavioral performance.
Results: SAPAP3 KOs were significantly impaired in reversal learning ($p<0.001$), with 40% of mutant mice failing to acquire a reversed contingency. Reversal learning-related cFos expression revealed correlated activity between the medial prefrontal cortex (mPFC) and the nucleus accumbens shell (NAcS) exclusively in SAPAP3-KOs, suggesting hyperconnectivity in this circuit. Dysfunction in this circuit profoundly influenced reversal performance in SAPAP3 KOs, whereby perseverative lever pressing on the previously active lever during reversal was influenced by mPFC and NAcS activity in a genotype-dependent manner.
Conclusions: Our studies are among the first to describe neurocognitive impairments in a transgenic OCD mouse model using a translational paradigm. These findings implicate aberrant neural activity in the mPFC-NAcS circuit, which is critical in the regulation of reward- and affective-related behaviors. SAPAP3 KOs will be a valuable model to examine the role of this circuit in a range of OCD-relevant cognitive and affective behaviors. Our results also suggest that to gain mechanistic insight regarding the role of cortico-striatal circuit dysfunction in OCD, it will be critical to use OCD-relevant cognitive paradigms in mouse models.

Disclosures: E.E. Manning: None. **M.M. Torregrossa:** None. **S.E. Ahmari:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.02/QQ21

Topic: H.01. Animal Cognition and Behavior

Support: NIH R21 MH096200

Title: The role of candidate gene Slc1a1 in ocd-relevant behaviors in mice

Authors: *J. M. KOPELMAN[1], I. D. ZIKE[3], K. F. TANAKA[4], J. VEENSTRA-VANDERWEELE[3], S. E. AHMARI[2]
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Psychiatry, Columbia Univ., New York, NY; [4]Dept. of Neuropsychiatry, Keio Univ., Tokyo, Japan

Abstract: Obsessive Compulsive Disorder (OCD) is a debilitating psychiatric disorder characterized by intrusive obsessive thoughts and compulsive behaviors. The cause of OCD is unknown, but human imaging studies have consistently shown hyperactivation of corticostriatal circuit nodes in patients with OCD. In addition, twin and family studies show a significant role for genetics in its etiology, with multiple studies identifying association of polymorphisms in the

gene *SLC1A1* with OCD. The most common of these OCD-associated polymorphisms increases expression of the encoded protein– the neuronal glutamate transporter, excitatory amino acid transporter-3 (EAAT3). This protein is expressed in OCD-relevant corticostriatal circuits, where it plays several roles, including modulating the activation of peri-synaptic glutamate receptors. The OCD-linked allele is associated with increased *SLC1A1* expression in lymphoblastoid cells, human postmortem brain, a luciferase reporter assay, and transfected HEK cells, where there is also a functional increase in EAAT3 protein activity, as evidenced by increased glutamate uptake. There is also increased EAAT3 protein expression in striatum of *Sapap3*-knockout (KO) mice, a model of OCD-like behavior. To directly test the effect of manipulations of EAAT3 levels on OCD-like behavior, we used the Flexible Accelerated STOP Tetracycline Operator-knockin (FAST) system, which combines cre, flippase, and tTA technology to create mice with either ablated or increased EAAT3 expression. *Slc1a1*-STOP knock-in mice that have ablated EAAT3 protein expression and function show blunted responses to pharmacologically-induced repetitive behavior. These mice have attenuated increases in stereotypy and hyperlocomotion in response to amphetamine and attenuated grooming increases in response to a dopamine D_1 receptor agonist (Zike et al, *PNAS*, in press). *Slc1a1*-Overexpressing (OE) mice were created by breeding *Slc1a1*-tetO mice with CamKII-tTA mice. *Slc1a1*-OE mice show increased striatal EAAT3 expression that can be normalized by the administration of doxycycline, allowing us to study the effects of temporally-specific EAAT3 overexpression. Here, we present data from the initial behavioral characterization of *Slc1a1*-OE mice, including OCD-relevant behaviors such as perseverative grooming, pre-pulse inhibition, and anxiety-like behavior.

Disclosures: **J.M. Kopelman:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Roche. **I.D. Zike:** None. **K.F. Tanaka:** None. **J. Veenstra-Vanderweele:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Roche. **S.E. Ahmari:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Roche.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

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Program#/Poster#: 164.03/QQ22

Topic: H.01. Animal Cognition and Behavior

Support: T32 MH016804

McKnight Foundation Neuroscience Scholar Award

BRAINS R01 MH104255

Burroughs Wellcome CAMS Award

The Pittsburgh Foundation

Title: Stimulation of medial orbitofrontal cortex terminals in ventromedial striatum causes neuroplastic changes in cortex

Authors: *J. WOOD[1], R. K. SNYDER[2], S. E. AHMARI[2]
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Abstract: Optogenetic stimulation of specific neuronal projections is a powerful tool for dissecting neural circuit function, but the network effects of axon terminal stimulation have not been thoroughly explored. To study these effects, we optogenetically stimulated medial orbitofrontal cortex (mOFC) projections in ventromedial striatum (VMS) while recording electrophysiological activity in mOFC networks during 10 days of repeated ChR2 stimulation. We observed that stimulation of terminals in VMS caused highly entrained population spikes in mOFC; single unit spikes did not occur during the inter stimulus interval (i.e. between light pulses).

To investigate the chronic effects of this synchronous entrainment, we measured pairwise cross correlations between mOFC neurons in 15-minute periods preceding and following stimulation. Prior to stimulation in session 1, there was no mOFC synchrony in ChR2 animals (0/66 pairs of simultaneously recorded mOFC neurons). Immediately following stimulation in the first session, 3% of mOFC neuron pairs had significant cross correlations. Synchrony continued to emerge in mOFC networks in association with repeated optogenetic stimulation. Prior to the final day of optogenetic stimulation (pre-stimulation period in session ten), 6.6% of mOFC pairs fired in synchronous fashion. Optogenetic stimulation on that day induced even greater levels of synchrony, such that 14.3% (13/91 pairs) of mOFC pairs fired synchronously. Significant pairwise synchrony was never detected in control mice.

These data demonstrate that terminal stimulation of corticostriatal projections causes antidromic activation and entrainment of mOFC, and that this activation induces neuroplastic changes in mOFC networks. These findings have broad implications for the effects of terminal stimulation on corticostriatal networks. The dissolution of distributed single unit spiking suggests that entrainment of recorded neurons was highly uniform, and potentially spread to non-VMS projecting neurons. Furthermore, because increased cortical synchrony is reflective of increased shared connections between neurons, these data raise the possibility that antidromic activation of corticostriatal projections induces a long-lasting change in connectivity within the cortex. Taken together, these findings provide evidence for a novel mechanism through which optogenetic stimulation of specific projections can alter circuit activity and plasticity in a broader manner than previously suspected.

Disclosures: J. Wood: None. **R.K. Snyder:** None. **S.E. Ahmari:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.04/RR1

Topic: H.01. Animal Cognition and Behavior

Title: Cortico-striatal molecular dysfunction in OCD post-mortem brain tissue

Authors: *S. E. AHMARI, B. CHAMBERLAIN, D. A. LEWIS, S. C. PIANTADOSI
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Abstract: BACKGROUND: Obsessive compulsive disorder (OCD) is a chronic, severe mental illness that affects 2-3% of people worldwide, and is a leading cause of illness-related disability. Brain imaging studies in patients with OCD have consistently shown abnormal activity in brain regions involved in decision-making (orbitofrontal cortex; OFC) and action selection (striatum). However, we have very little knowledge regarding the molecular changes in these brain regions that contribute to abnormal function in people who suffer from OCD. The goal of the present study was to examine expression of several candidate post-synaptic density genes in relevant cortico-striatal brain regions (OFC and striatum) obtained from subjects with OCD and matched comparison subjects.
METHODS: High-quality post-mortem brain samples from matched pairs (n = 8 pairs) of unaffected comparison subjects and OCD subjects were obtained through the University of Pittsburgh Brain Tissue Donation Program. Grey-matter tissue samples were obtained from 4 brain regions: medial OFC (BA11), lateral OFC (BA47), head of caudate nucleus, and nucleus accumbens core (NAcc). Quantitative polymerase chain reaction (qPCR) was then performed on a panel of excitatory and inhibitory mRNA transcripts.
RESULTS: Relative to matched unaffected comparison subjects, OCD subjects had significantly lower expression of many key excitatory transcripts in both medial and lateral OFC. These transcripts included several family members of the post-synaptic density protein *DLGAP*, several members of the *SLITRK* transmembrane protein family, and critical glutamate receptors often found at the post-synaptic density (*GRIA1, GRIN2B*). A significant decrease in expression of *SLC1A1*, which encodes one of several glutamate transporters key to the normal function of excitatory synapses, was also observed in OFC of OCD subjects. By contrast, few transcripts were changed in either caudate nucleus or NAcc. However, in each region there was a significant decrease in *DLGAP3*, making it the only transcript affected across all four cortico-striatal regions.
CONCLUSIONS: Gene expression analysis of post-mortem tissue from OCD subjects and matched comparison subjects showed a consistent down-regulation of genes involved in excitatory signaling within the OFC. *DLGAP3*, which encodes for a post-synaptic scaffolding protein, was reduced across all regions in OCD subjects. Surprisingly, few other significant

changes in gene expression were observed in striatum of OCD subjects. Future planned experiments include targeted proteomics and phospho-proteomics of the post-synaptic density in OFC and striatum of OCD subjects.

Disclosures: S.E. Ahmari: None. **B. Chamberlain:** None. **D.A. Lewis:** None. **S.C. Piantadosi:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.05/RR2

Topic: H.01. Animal Cognition and Behavior

Support: 5F32MH108226

R01MH104255

MQ Fellows Award

Title: *In vivo* calcium imaging of SKF38393 induced perseverative grooming in awake behaving mice

Authors: *J. R. HYDE[1], S. E. AHMARI[2]
[1]Translational Neurosci. Program, [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Obsessive compulsive disorder (OCD) is characterized by intrusive obsessive thoughts and abnormal repetitive behaviors. Studies of several independent mouse models of OCD-like behavior suggest that perseverative grooming in mice is related to compulsive behaviors seen in OCD. Understanding the mechanisms leading to the development of abnormal grooming is therefore relevant to OCD pathophysiology. However, the changes in cellular activity that are correlated with the development of perseverative grooming are unknown. Using miniaturized head-mounted microscopes and calcium imaging, we therefore examined changes in cellular activity in the ventromedial striatum (VMS) during pharmacologically- induced perseverative grooming behavior. Drd1a-tdTomato mice were injected with the genetically encoded calcium indicator AAV9.hsyn.GCaMP6m and implanted with a microendoscope (6.1mm x 0.5mm GRIN lens) in VMS. Four weeks after virus injection, mice were fitted with a microscope baseplate. Upon recovery, behavioral experiments were performed. Using a cross-over within subjects experimental design, mice were treated with either vehicle or the D1 agonist, SKF38393, to induce perseverative grooming. Both behavior and calcium signaling were monitored continuously for 10 minutes prior to injection and 30 minutes post injection. Calcium data were extracted from processed videos to analyze event frequency and time-locked activity; both PCA/ICA and CNMF algorithms were used. As expected, grooming activity

increased after SKF38393 injection in VMS implanted mice. However, we also found that SKF38393 selectively induces increased grooming activity only during the facial grooming steps of a stereotyped grooming chain. *In vivo* microendoscopy demonstrated that average calcium event rates decreased during facial grooming regardless of SKF38393 or saline treatment. However, event rates selectively increased during non grooming and body grooming periods in SKF treated mice. Event rates during saline control experiments showed no differences between grooming and non-grooming time periods. These results suggest selective changes in striatal firing patterns as well as changes to initiation, transition, and cessation of grooming behavior after SKF38393 treatment. Ongoing analysis is delineating the precise relationship between changes in network level activity and bouts of perseverative grooming, and determining whether the SKF-induced differences in event rates during non-grooming time periods are related to transitions into and out of grooming bouts.

Disclosures: J.R. Hyde: None. **S.E. Ahmari:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

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Program#/Poster#: 164.06/RR3

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant R00 NS076524-03

NIH BRAINS R01MH104255

Burroughs Wellcome Career Award for Medical Scientists

NIH F31 MH110125

Title: Dysregulation of cortical inputs to central striatum play a role in compulsive-like grooming in Sapap3-KO mice

Authors: *V. L. CORBIT[1], A. H. GITTIS[3], S. E. AHMARI[2]
[2]Psychiatry, [1]Univ. of Pittsburgh, Pittsburgh, PA; [3]Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Obsessive-Compulsive Disorder (OCD) is defined by the inability to suppress compulsive thoughts and behaviors. The exact neuronal mechanisms underlying these symptoms are unclear; however, hyperactivity in corticostriatal circuits is consistently observed in OCD patients. Specifically, circuits involving the lateral orbitofrontal cortex (LOFC) are dysfunctional in OCD patients, and homologous corticostriatal circuitry has been shown to be dysregulated in the Sapap3-KO OCD mouse model. It has also been suggested that there may be dysfunction in

striatal fast-spiking interneurons (FSIs), which are thought to play a role in abnormal behavioral suppression through their regulatory influence on striatal output neurons (MSNs). Both FSIs and MSNs are driven primarily by cortical inputs. Thus, investigating how LOFC influences striatal FSIs and MSNs is essential to understanding how corticostriatal microcircuits contribute to compulsive behaviors. To determine how LOFC inputs regulate microcircuits in central striatum (CS), we injected channelrhodopsin2 (ChR2) into cortex and recorded optogenetically-evoked excitatory post-synaptic currents (EPSCs) using acute slice physiology. LOFC-evoked EPSCs onto MSNs were weaker in KO mice relative to WTs, while LOFC inputs to FSIs were unchanged. The ratio of EPSC amplitudes confirmed that LOFC input to FSIs is increased relative to nearby MSNs, suggesting LOFC evoked feedforward inhibition is stronger in Sapap3-KOs. These results demonstrated a more complex dysfunction of corticostriatal circuitry than was expected and suggested another cortical input to CS, supplementary motor region M2, may also be dysregulated in Sapap3-KOs. We found that M2-evoked EPSCs were increased onto both MSNs and FSIs in the CS of Sapap3-KOs relative to WTs, indicating a general increase in CS drive from M2. In vivo inhibition of M2 reduced grooming behavior in Sapap3-KOs, but not WT littermates, suggesting that hyperactivity in M2-CS circuits may play a role in abnormal behavioral selection in Sapap3-KO mice. These data suggest that primary cortical control of CS may shift from LOFC to M2, potentially causing the repetitive grooming behavior seen in the Sapap3-KO mice. These results bring new focus to the role of supplementary motor cortical regions in the pathology of OCD. Moreover, increased relative drive to CS FSIs suggests that interneuron dysfunction may play a role in abnormal behavioral selection and initiation mechanisms relevant to OCD. Taken together, these results reveal corticostriatal abnormalities that may cause compulsive behaviors in OCD.

Disclosures: V.L. Corbit: None. **A.H. Gittis:** None. **S.E. Ahmari:** None.

Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

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Program#/Poster#: 164.07/RR4

Topic: G.07. Other Psychiatric Disorders

Support: Washington & Lee University

Title: Compared to male rats, female rats display increased OCD-like compulsive behaviors in the Hole Board and Marble Arena and decreased anxiety behaviors in the Elevated Plus Maze

Authors: *J. L. STEPHENS[1], E. CHARTAMPELIA[1], A. T. DANGLER[1], E. D. ELLIS[1], H. L. PALMATARY[1], D. S. KREISS[1,2]
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Abstract: Although the importance of the role of sex on the expression of medical disorders has been recognized for some time, until recently there has been little transference of this recognition in research utilizing animal models. This study was inspired by the new appreciation for the limitations of a male-only approach when investigating psychiatric disorders, especially for disorders like Obsessive Compulsive Disorder (OCD) that present equally in both sexes. OCD is characterized by persistent, anxiety producing thoughts accompanied by overwhelming urges to perform repetitive, ritualistic behaviors. Current pharmacological treatments for OCD are problematic: they are effective in only 40-60% of patients, have an 8-10 week delayed onset, and are associated with troublesome side effects. Identification of animal behaviors that model the symptoms of this debilitating disorder would provide an invaluable research tool for the development of new avenues of treatment. The current study evaluated potential sex differences in adult rats (Day 90-107) by comparing the expression of "OCD-like" behaviors in female (n=24) versus male (n=15) rats in the Hole Board, Marble Arena, and Elevated Plus Maze (EPM). Previous studies from the Kreiss lab have demonstrated that these behaviors have both face and predictive validity in the neonatal clomipramine animal model of OCD. Significant differences between the sexes were observed in all 3 behavioral arenas. In the Hole Board, female rats had higher pokes per hole than did males ($p=0.028$). In the Marble Arena, female rats displayed more marble checks ($p=0.022$), and fewer marble buries ($p=0.006$). In the EPM, female rats spent more time in the open arms ($p=0.029$), had increased open arm entries ($p=0.009$), and entered more total arms ($p=0.010$). These results demonstrate that compared to male rats, females display more OCD-like behaviors in the Hole Board and Marble Arena, while expressing a lower level of anxiety-like behaviors in the EPM. This study demonstrates that Hole Board and Marble Arena can be utilized to discriminate OCD-like behaviors versus anxiety-like behaviors and, moreover, contributes to the understanding that fundamental differences between sexes of animals significantly influence the expression of behaviors that model OCD and other anxiety-related disorders.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.08/RR5

Topic: G.07. Other Psychiatric Disorders

Support: Washington and Lee University

Title: Who's your daddy? Transgenerational epigenetic effects of the neonatal clomipramine rodent model of obsessive compulsive disorder

Authors: *C. C. DAVIS[1], K. W. SINGERMAN[1], S. J. BELFORTI[1], A. K. FERRERO[1], A. A. WUBAH[1], D. S. KREISS[1,2]
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Abstract: Obsessive Compulsive Disorder (OCD) is characterized by worrisome thoughts accompanied by overwhelming urges to perform repetitive behaviors. Modern pharmacological treatments for OCD are only effective in 40-60% of patients, have an 8-10 week delayed onset, and are associated with problematic side effects. It is currently unknown whether OCD is one of many neurological illnesses affected by transgenerational epigenetics, an environmentally induced change in the parental DNA altering offspring either via the sperm or egg. The objective of the current study was to investigate whether transgenerational epigenetic effects would be expressed in an animal model of OCD induced by neonatal exposure to clomipramine, a serotonin/norepinephrine uptake inhibitor. Prior studies from the Kreiss lab have demonstrated that the neoclomipramine model has both face and predictive validity in the Hole Board (HB), Marble Arena (MA), and Elevated Plus Maze (EPM). Behaviors in the HB, MA, and EPM were assessed in naïve adult male offspring of father rats who were injected neonatally (Day 9-16) with either 15 mg/kg clomipramine (neoCLOM offspring, n=14) or with saline (neoSAL offspring, n=15). Significant results were found in all three arenas. In the HB, neoCLOM offspring had a lower poke:hole ratio ($p=0.016$) and fewer repeated pokes ($p=0.025$). In the MA, neoCLOM offspring displayed fewer marble checks ($p=0.005$), fewer lifts ($p=0.037$), and fewer buries ($p=0.002$). In the EPM, neoCLOM offspring spent less time in the open arms ($p=0.006$), had fewer open arm entries ($p=0.014$), and had fewer total arm entries ($p=0.031$). One interpretation of this data is that the neoCLOM offspring have decreased activity compared to the neoSAL offspring. Another interpretation of this data is that the neoCLOM offspring have significantly less "OCD-like" behaviors in the HB and MA and more anxiety-like behavior in the EPM. If the latter interpretation is valid, then the current study provides evidence that transgenerational epigenetic effects attenuated the expression of OCD-like behaviors and potentiated the expression of anxiety-like behaviors. Either way, this study demonstrates that neonatal exposure to clomipramine causes epigenetic changes that impact future generations via the male germ line. This finding is in accordance with both clinical and animal studies that have shown parental epigenetic alterations can influence the behaviors of offspring by increasing the expression of certain traits while decreasing the expression of others. In other words, transgenerational epigenetic effects may significantly influence both vulnerability and resiliency to environmental stressors.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

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Program#/Poster#: 164.09/RR6

Topic: G.07. Other Psychiatric Disorders

Support: Wellcome Trust Seed Award in Science 200710/Z/16/Z

Title: The influence of pavlovian memories on a rodent model of compulsive checking relevant to obsessive-compulsive disorder

Authors: *A. L. MILTON, G. H. VOUSDEN, S. PAULCAN, D. M. EAGLE, T. W. ROBBINS
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Abstract: In obsessive-compulsive disorder (OCD), behaviors that are initially functional become maladaptive and debilitating. Compulsive checking is commonly observed in OCD, and can be modelled in rats using the observing response task (ORT). In the ORT, rats use one (checking) lever to determine which of two other, unpredictably reinforced, levers is currently rewarded. Therefore, the ORT allows for the performance of functional - providing information about uncertain reinforcement contingencies - and dysfunctional checking, as additional responses on the checking lever provide no further information and distract the animal from responding for reinforcement.
OCD has traditionally been conceptualized as a disorder in which obsessive thoughts provoke extreme anxiety and compulsive performance of rituals provides relief. An alternative view is that the development of compulsions in OCD is similar to compulsive habits in addiction, depending on the appetitive motivational system. Based on our previous data, we hypothesized a dissociation in the motivational systems that influence the development of functional and dysfunctional checking, with anxiogenic CSs promoting the development of functional behaviors to reduce uncertainty, and appetitive CSs supporting the conversion of these behaviors into dysfunctional, maladaptive responses.
In the current study, prior to ORT training, male rats received training on a pavlovian autoshaping procedure associating presentation of the checking lever and reward (n = 37), or a control task (n = 10). Following ORT training, responding under uncertain (VI10-20s) reinforcement was assessed. Rats in the autoshaping group showed greater levels of dysfunctional checking as measured by additional responses on the observing lever compared to controls, supporting our hypothesis that appetitive motivational processes underlie dysfunctional checking behavior. Finally, to investigate the interaction between appetitive and aversive motivational processes in checking behavior, all animals underwent pavlovian fear conditioning in a distinct context containing portable elements. They subsequently underwent testing in a ‘probe’ version of the ORT in which elements of the aversive context were presented, to

determine the additional impact of aversive pavlovian stimuli on checking.
These findings provide insight into the influence of pavlovian memories on the development of functional, and subsequently dysfunctional, checking behavior relevant to OCD.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

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Support: Medical Research Council grants G0300155

MRC UK Autism Imaging Multicentre Study G0400061

Ph.D. studentships from the Institute of Psychiatry, Psychology and Neuroscience, King's College London

NIHR-BRC PhD studentship

Title: Shared and disorder-specific neurocomputational mechanisms of decision-making in autism spectrum disorder and obsessive-compulsive disorder

Authors: *C. O. CARLISI[1], L. J. NORMAN[1], C. M. MURPHY[1], A. CHRISTAKOU[2], K. CHANTILUKE[1], V. GIAMPIETRO[1], A. SIMMONS[1], M. BRAMMER[1], D. G. MURPHY[1], D. MATAIX-COLS[3], K. RUBIA[1]
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Abstract: Autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD) are often comorbid and share phenotypes of repetitive behaviours, possibly underpinned by abnormal decision-making. However, no studies have compared the neural correlates of decision-making in these disorders. Brain-activation of boys with ASD (N=24), OCD (N=20) and typically-developing controls (N=20) during the Iowa Gambling Task was compared, and computational modelling compared performance. Patients were unimpaired on number of risky decisions, but modelling showed that both patient groups had lower choice consistency and relied less on reinforcement learning compared to controls. ASD patients had disorder-specific choice perseverance abnormalities. Neurofunctionally, ASD and OCD boys shared left dorsolateral and right inferior frontal underactivation compared to controls during decision-making. During

reward/loss outcome anticipation, patients shared underactivation in left lateral-inferior/orbitofrontal cortex and right ventral striatum. During reward receipt, ASD boys had disorder-specific enhanced activation in left inferior frontal/insular regions relative to OCD boys and controls. This study showed that ASD and OCD individuals use different decision-making strategies to perform comparably to controls. Patient groups showed shared abnormalities in lateral-(orbito)fronto-striatal circuitry linked to reward processing, but ASD boys had disorder-specific lateral inferior frontal/insular overactivation, suggesting that both shared and disorder-specific neurofunctional mechanisms underpin decision-making in these disorders.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.11/RR8

Topic: G.07. Other Psychiatric Disorders

Support: Tourette Association of America

Title: Juvenile onset of stereotypy with loss of BDNF signaling in D1R expressing striatal neurons

Authors: *M. ENGELN[1], R. CHANDRA[1], A. LA[1], Y. SONG[2], B. EVANS[1], T. C. FRANCIS[1], R. HERTZANO[3], M. LOBO[1]
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Abstract: Imbalance between D1- vs. D2-receptor containing medium spiny neuron (MSN) basal ganglia output-pathways is implicated in stereotyped disorders such as Tourette Syndrome (TS) and obsessive-compulsive disorder (OCD). Surprisingly, there is little information on the molecular role of MSN subtypes in stereotypy disorders. We have a mouse model with a deletion of TrkB (the BDNF receptor) in D1-MSNs (D1-Cre-flTrkB mice), in which a subset of mice display involuntary stereotypic behaviors beginning around 3 weeks of age. We first characterized repetitive behaviors in D1-Cre-flTrkB mice with stereotypy (S), or with no stereotypy (NS), and D1-Cre control mice. Complete turns, head tics, rearing, and grooming are assessed weekly from ages 3 to 8 weeks. We found that D1-Cre-flTrkB-S mice display more complete turns at all ages compared to D1-Cre-flTrkB-NS and control mice. D1-Cre-flTrkB-S mice exclusively display head tics, which decline from juvenile to adult ages. We then selectively inhibited dorsal striatum D1-MSNs using Designer Receptors Exclusively Activated

by Designer Drugs (DREADDs; AAV-DIO-HM4D(Gi)-mCherry) to evaluate if abnormal D1-MSN activity is responsible for stereotypic behaviors. Our data suggest that selective inhibition of D1-MSNs with DREADDs reduces circling behavior. To get further insight into the molecular alterations in D1-MSNs of mice with stereotypy, we crossed D1-Cre-flTrkB mice with flRiboTag (RT) mice to extract cell-type specific mRNA from D1-MSNs. We then conducted cell-type specific RNA-sequencing on D1-Cre-flTrkB-RT-NS, D1-Cre-flTrkB-RT-S and D1-Cre-RT mice. Transcriptome analysis revealed differential gene expression between all groups and gene ontology analysis highlighted significant changes in gene expression between mice with and without stereotypy for genes involved in dendritic development and synaptic function. These results led us to evaluate D1-MSN morphology. Our preliminary studies suggest altered neuronal morphology in mice with stereotypy exclusively. These alterations could support dysfunctional activity in D1-MSNs. Our ongoing work can provide novel insight into the cell subtypes and molecular mechanisms underlying stereotypy disorders.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

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Program#/Poster#: 164.12/RR9

Topic: G.07. Other Psychiatric Disorders

Support: FAPESP 2011/21357-9

FAPESP 2013/04741-5

Title: mCPP-induced grooming behavior and fear extinction: Possible relation with obsessive-compulsive disorder

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Abstract: Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by intrusive thoughts (obsessions) and rituals (compulsions), that affects 2-3% of the population. Although OCD pathophysiology is not fully elucidated, clinical studies and animal models strongly suggest a serotonergic dysfunction in this disorder. In this direction, the serotonergic agonist meta-chlorophenylpiperazine (mCPP) worsens symptoms in untreated OCD patients and

exacerbates repetitive behaviors in rodents. In this context, self-grooming behavior has often been associated with an OCD-like condition in animal models. Since recent evidence have indicated that OCD patients present important impairments in extinction retention of conditioned aversive memories, in the present study we evaluated mCPP-induced grooming in rats and its influence on the expression and extinction of conditioned fear. For this, male Wistar rats were submitted to a contextual fear conditioning training (10 footshocks-US; 1 s; 0.6 mA) and, prior to the first or each of the three extinction sessions (10 min of re-exposure to the aversive context), animals received intraperitoneal administration of mCPP (0.0, 0.5, 1.0 or 3.0 mg/kg). Grooming behavior and immobility were scored for 20 min immediately after drug treatment. Conditioned freezing behavior was evaluated for 10 min in each one of four extinction sessions. To further evaluate the existence of a link between grooming prevalence and OCD physiopathology, a different set of animals was submitted to the marble burying test, previously proposed as a model of compulsive behavior. mCPP increased grooming expression, but did not affect immobility. When single administered, mCPP had no effect on fear expression or extinction. However, when administered before each extinction session, mCPP impaired extinction recall. No correlation was found between grooming expression and compulsive-like burying behavior. In general, present data indicate that mCPP-exacerbated grooming behavior is associated with impaired fear extinction, suggesting that this pharmacological model is consistent with an OCD-like profile in animals.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 164.13/RR10

Topic: G.07. Other Psychiatric Disorders

Title: Altered habit formation in Sapap3 knockout mice

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Abstract: Compulsivity manifests itself as the urge to perform a behavior irrespective of its negative consequences and the experience of loss of voluntary control. As compulsive behaviors are often performed in a repetitive and habitual manner, it has been hypothesized that maladaptive habit formation contributes to development or maintenance of compulsivity in psychiatric disorders such as obsessive-compulsive disorder (OCD). To investigate if the balance between goal-directed and habitual behavior is altered in an established animal model of OCD,

we tested 24 Sapap3 knockout mice and 24 wildtype littermate (WT) controls in a habit formation task. In this task, two different schedules of reinforcement are used to discriminate between behavioral strategies in an outcome devaluation test: a random-ratio (RR) reinforcement schedule promotes goal-directedness, whereas a random-interval (RI) schedule facilitates habitual responding. A within-subject design was used to measure individual response strategies (animals were subjected to both schedules in different environments). Our results show that WT mice were sensitive to outcome devaluation following training under RR, but not RI schedules, indicating flexible switching between goal-directed and habitual response strategies. In contrast, Sapap3 knockout mice were sensitive to outcome devaluation after both, RR and RI reinforcement training. This suggests decreased employment of habitual response strategies in Sapap3 knockout mice. Such diminished habitual responding is a disadvantage in situations that demand behavioral automation and habitual responding. In addition, our study revealed lower response rates and fewer attempts to collect rewards in Sapap3 knockout compared to WT mice. This may indicate altered reward processing in Sapap3 knockout mice during specific conditions of appetitive learning, which requires further investigation. Together, our findings suggest that less efficient habit learning and altered reward processing should be considered as contributing factors in the development of compulsivity in clinical conditions, such as OCD.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

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Support: Hundred Talent Program of the Chinese Academy of Sciences (Technology), Strategic Priority Research Program (B) of the Chinese Academy of Sciences (XDB02050000)

National Natural Science Foundation of China Grant (81571300, 81527901, 81271518, 81471387)

Title: A robust evaluation of morphologic alterations in obsessive-compulsive disorder with and without pharmacological interventions

Authors: Q. LV[1], Z. WANG[2], C. ZHANG[3], Q. FAN[2], Q. ZHAO[2], K. ZELJIC[1], B. SUN[3], Z. XIAO[4], *Z. WANG[1]
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Abstract: Objective: Serotonin reuptake inhibitors have been widely used as first-line pharmacologic intervention for obsessive-compulsive disorder (OCD); however, neural mechanisms that underlie their efficacy/inefficacy have not yet been fully established. Prior efforts to dissect etiological and pharmacological complications in brain morphologic changes are undermined by methodological and sampling constraints, yielding no reproducible and reliable neuromarkers for improved clinical utility. Method: 334 participants were enrolled between April 2, 2013 and April 13, 2016. Pathological alterations of regional gray matter volume including effect size (Cohen's d value) were first estimated in a subgroup of drug-naïve OCD patients (N = 96) by comparison with healthy subjects (N = 96). In regions with statistically significant group differences and considerable effect size, we examined pharmacologic effects in two OCD subgroups: medicated (N = 66) and medication-free (N = 76). Robustness of statistical outcomes and effect sizes was rigorously tested with Monte Carlo cross-validation. Results: Relative to controls, drug-naïve and medication-free patients both exhibited comparable increases in volume mainly in the left thalamus, left ventral striatum, bilateral medial orbitofrontal cortex, and left inferior temporal gyrus, and decreased volumes in left premotor/presupplementary motor areas. Interestingly, structural abnormalities in premotor and ventral striatum areas were largely rectified by serotonin reuptake inhibitors that were almost ineffective in the thalamus and medial orbitofrontal cortex. Conclusions: Divergent structural responses in orbitofronto-striato-thalamic and premotor circuits are characteristic of serotonergic-based drug treatment in OCD. This cross-validated dissection of circuit-level therapeutic effects provides a candidate predictive neuromarker for future advancement in stratified medicine practice.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

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Program#/Poster#: 164.15/RR12

Topic: G.07. Other Psychiatric Disorders

Support: NIH Grant MH081060

Title: MeCP2 and histone deacetylases 1 and 2 in dorsal striatum collectively suppress repetitive behaviors

Authors: *M. MAHGOUB[1], M. ADACHI[1], K. SUZUKI[1], X. LIU[1], E. T. KAVALALI[1,2], M. H. CHAHROUR[1,3], L. M. MONTEGGIA[1]
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Abstract: Class I histone deacetylases (HDACs) Hdac1 and Hdac2 can associate together in protein complexes with transcriptional factors such as methyl-CpG-binding protein 2 (MeCP2). Given their high degree of sequence identity, we examined whether Hdac1 and Hdac2 were functionally redundant in mature mouse brain. We demonstrate that postnatal forebrain-specific deletion of both *Hdac1* and *Hdac2* in mice impacts neuronal survival and results in an excessive grooming phenotype caused by dysregulation of *Sap90*/*Psd95*-associated protein 3 (*Sapap3*; also known as *Dlgap3*) in striatum. Moreover, Hdac1- and Hdac2-dependent regulation of Sapap3 expression requires *MECP2*, the gene involved in the pathophysiology of Rett syndrome. We show that postnatal forebrain-specific deletion of *Mecp2* causes excessive grooming, which is rescued by restoring striatal *Sapap3* expression. Our results provide new insight into the upstream regulation of *Sapap3* and establish the essential role of striatal Hdac1, Hdac2 and MeCP2 for suppression of repetitive behaviors.

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Poster

164. Animal Models: Obsessive-Compulsive Disorder

Location: Halls A-C

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Program#/Poster#: 164.16/RR13

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant P20GM103645

DEANS Award, Brown University

Title: Obsessive-compulsive disorder and brain activation during changes in action intention

Authors: P. BÉDARD[1], S. L. GARNAAT[2], B. D. GREENBERG[2,3], *J. N. SANES[1,3]
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Abstract: Obsessive-compulsive disorder (OCD) is marked by intrusive thoughts and repetitive ritualistic actions that often exclude goal-directed behaviors, suggesting possible impairment in using external or internal cues. We examined adaptive flexibility in OCD by studying brain activation during a “Change-of-Mind” (CoM) task and a task that required changing intended movement end-point using external cues. We hypothesized that OCD would affect brain activity in frontal-striatal brain networks compared to controls. We recruited adult patients with a DSM-IV diagnosis of OCD along with clinical significant OCD symptoms and healthy adults. For the CoM task, participants viewed a random-dot pattern that had varying coherence levels and moved their arm to "capture" one of two targets based on the perceived display motion. For the

visually guided tasks, participants performed direct movement to a target; a via-point movement requiring an arced movement passing through an intermediate point; and a target jump task that required participants to change their intended movement direction by shifting the end-point target immediately after movement onset. We measured BOLD signals during all tasks using a 3T Siemens Prisma. We used a standard two-stage analysis strategy to assess group-level differences between conditions. For the CoM task, OCD patients and controls changed the direction of their initial movement on a small percentage of events. The OCD patient group exhibited about one-half the proportion of CoM events than controls. During CoM events, the OCD patient group exhibited less activation than controls in the pre-genual region of the anterior cingulate and prefrontal cortex anterior to this cingulate region, but showed more activation than controls in a posterior cerebellar region. For the three target jump tasks, OCD patients and controls had similar behavior. For the direct and via-point tasks, we found similar brain activation patterns for the OCD patients and controls. By contrast, OCD patients showed less activation in the lingual gyrus, superior parietal lobule, medial thalamus, and an anterior cerebellum region during the actual target-jump events. The current results demonstrate brain activation differences between OCD patients and age-matched controls when action intentions become modified due to internal and external influences, but only behavioral differences for internally generated changes in action intention. OCD patients showed lower activation in frontal regions that have interconnections with striatal structures implicated in OCD, suggesting that these neocortical regions could represent targets for therapeutic intervention.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.01/RR14

Topic: G.06. Post-traumatic Stress Disorder

Title: Post-traumatic stress disorder in the controlled cortical impact model of brain injury

Authors: A. M. CHOO, S. DAVIS, M. LANG, A. BARBOZA, A. HACKETT, W. ALVINS, M. OSBORNE, Q. CHANG, *T. HANANIA
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Abstract: Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are often associated with each other. Comorbidity of TBI and PTSD are often seen in military populations. It is estimated that 35% of returning veterans suffer from both PTSD and TBI. Currently, there is no standardized preclinical model of PTSD with traumatic brain injury. We studied the development of PTSD behavioral phenotypes by combining two widely used preclinical models

of PTSD and TBI: immobilization stress and controlled cortical impact in rats. Following 1 week of incubation after immobilization, stressed animals exhibited a significant increase in open arm entries and spent more time in the open arms of the elevated plus maze which was suggestive of an increase in risk-taking behavior. This risk-taking phenotype was observed to subside to similar levels as non-stressed controls by 2 weeks after immobilization. If instead, animals received TBI after immobilization stress, the risk-taking phenotype remained significantly elevated at this 2 week time point. In fear conditioning test, animals that received TBI-only showed similar freezing to non-stressed navie animals during tone and shock exposure. In contrast, animals that received only immobilization stress exhibited potentiated freezing during training while animals that received both immobilization stress and TBI exhibited less freezing. In the tone cue test, the group that received both immobilization stress and TBI again showed the lowest levels of freezing. These results suggest that the predominant phenotype of combined immobilization stress with controlled cortical impact brain injury is heightened activity and risk-seeking behavior during the sub-acute period following stress and TBI. This model may be useful for studying the evolution of preclinical stress-TBI phenotypes over time.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

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Program#/Poster#: 165.02/RR15

Topic: G.06. Post-traumatic Stress Disorder

Support: DGAPA-PAPIIT 305715

PAPIME PE300715

Title: Different sources of stress: Sex and model type differences

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Abstract: Stress-related mental illnesses could be related to the nature and duration of the stressor. Excessive and prolonged stress can lead to neuronal damage in vulnerable brain structures, such as the hippocampus, that is reflected with a potential negative impact on learning and memory function. Chronic restraint stress alters hippocampal-dependent spatial learning and memory in male rats, whereas in females the performance was intact or better. On the other hand, the acute stress exposure (ex. predator scent stress model, PSS) can modulates learning and memory processes. Rodents that were exposed to PSS showed impairment on spatial memory retrieval, independent of sex or strain tested on radial arm maze. This suggests that sex and stressor type influences the effects of stress. The aim of this study was to compare two different stressors vs. no-stress condition: CUS, PSS, and control group, respectively. Male and female Wistar rats four months old were used (n=10 per group). Animals of CUS group were exposed to a Chronic Unpredictable Stress Battery (CUSB) for ten days. The stressors that made up the battery consisted of 1) placing animals in movement restrictors for 20 min. (3 times per day), 2) swimming in cold water for five minutes (16°C), 3) overnight light exposure (12 hours), 4) placing the rats for 20 hours (overnight) in their home cages with wet bedding, 5) placing the rats for 3 hours in their home cage that was tilted at 45°, and 6) overnight water deprivation (12 hours). The exposure to each stressor was randomized according to the CUSB protocol. Animals of the PSS group were exposed for 10 minutes in an exposure box that contained a bottle of sand impregnated with predator urine. Behavior was assessed with Barnes Maze Test 24 hours after the final stressor exposure. The results of latency for escape were not significant between groups or sex. Nevertheless, it was observed that females had more number of errors compared with males but not between stress conditions. Finally, those results are consistent with an impairment in spatial memory processes.
Word Keys: stress, spatial memory, rats, PSS, CUS.
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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.03/RR16

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH R01MH098003

Title: Characterization of predator odor scent stress using a behavioral battery and exploration of inheritance of behavioral phenotypes in Long Evans rats

Authors: *D. DOPFEL, A. VERBITSKY, T. SCHLAMB, N. ZHANG
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Abstract: Post-traumatic stress disorder (PTSD) is a complex phenotype making it difficult to model in rodents. On top of this complexity there are environmental and genetic factors that strongly influence the development of this phenotype. Typically, a long-term heightened anxiety level is prioritized while other diagnostic criteria of PTSD have been less well studied. To fill this gap in our understanding of rodent models of PTSD, a behavioral battery was performed in order to assess rodent behavior to a more complete diagnostic criterion of PTSD. Furthermore, offspring of these rats were tested using the same experimental design to look at possible heritability of behavior and susceptibility. To do this we utilized the predator odor scent exposure model, one of the more commonly used and well accepted rodent models of PTSD. Single-episode predator odor exposure was conducted with rats randomly divided into control and predator odor groups. The predator odor group was exposed to cotton sprayed with fox urine while the control group was exposed to unscented cotton. The exposed rats were then separated into vulnerable and resilient groups based on the behavioral measures. These rats were then bred with naïve female rats to avoid an effect due to maternal care. These offspring were then similarly separated into control and predator odor groups and run through the behavioral battery. With this we were able to explore the relevance of genetic and epigenetic influences on behavioral and susceptibility measures by comparing offspring behavior with paternal behavior and stress exposure. The behavioral measures used include measures of anxiety, arousal, avoidance and affect to account for the different criterion used to diagnose PTSD. A number are also performed pre- and post-stress allowing for a better understanding of the change in behavior due to the stress response and hinting at the possibility of predictive behavioral phenotypes of susceptible rats. This behavioral battery included latency to a novel object (physical and social), acoustic startle response (ASR), pre-pulse inhibition (PPI), elevated plus maze (EPM), light dark box (LDB), marble burying, novelty suppressed feeding and sucrose preference. This work will allow for a more productive rodent model of PTSD to be developed by better understanding the behavioral effects of stress and the relative impact of genetic and epigenetic inheritance of PTSD relevant traits.

Disclosures: **D. Dopfel:** None. **A. Verbitsky:** None. **T. Schlamb:** None. **N. Zhang:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R01MH098003

NIH Grant R01NS085200

Title: Studying a post-traumatic stress disorder rat model with awake resting-state fMRI and behavior techniques

Authors: *P. D. PEREZ[1,2], D. DOPFEL[1,2], N. ZHANG[1,2]
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Abstract: A strong stress response occurs when an individual is exposed to a situation that is perceived as an imminent threat to its safety. A single life-threatening experience that overwhelms the individual emotional or physical resources, in the event of maladaptation, can develop in chronic stress related disorders such as post-traumatic stress disorder (PTSD), anxieties and phobias. The mechanisms of PTSD are not well understood. Furthermore, there is heterogeneity in the response to traumatic stress and its eventual development in a chronic disorder. Most studies in humans have focused on restricted populations that had already been exposed to variable uncontrolled events of traumatic stress months or years ago, such as accident or crime victims and war veterans. The use of animal models allows for the longitudinal investigation of PTSD at various points in time, including the stage before the traumatic stress which is very difficult to observe in humans. We present a rat model where a single-event is used in the form of predator scent in an inescapable environment. Using behavior and awake resting-state functional magnetic resonance imaging (rsfMRI) techniques, we can study the heterogeneous responses in the exposed population at the behavioral and neuronal circuit level which allows for the segregation of resilient and vulnerable subpopulations. Behavioral methods are used to evaluate anxiety and the efficacy of trauma. Furthermore, we explore how stress modulates fear conditioning and extinction which are believed to be staples of chronic stress disorders. Using rsfMRI in the awake condition, we can avoid the confounding factors of anesthetics, obtain data more representative of the affective state of the subject and observe neuroplasticity changes produced by trauma at the circuit level.
Our longitudinal set of experiments has multiple goals. We first investigate the impact of controlled single-episode trauma and the onset of chronic stress disorder. We then investigate its effects in fear conditioning and later fear extinction processes. Furthermore, we observe a segregation of resilient and vulnerable populations. By looking at differences between these two populations at different stages, we study the existence of behavioral and neuroimaging vulnerability indicators of PTSD with non-invasive techniques. Understanding and detecting this vulnerability has great importance in prevention and treatment, and it opens the way for later extending this knowledge to human studies.

Disclosures: **P.D. Perez:** None. **D. Dopfel:** None. **N. Zhang:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

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Program#/Poster#: 165.05/RR18

Topic: G.06. Post-traumatic Stress Disorder

Support: College of Health Sience,University of Kwazulu-Natal

Title: Changes in Neurotrophic factors and PKB/AKT in the striatum and cerebellum in a rat model of posttraumatic stress disorder (PTSD): A relevance for movement disorders

Authors: *G. T. NGOUPAYE[1,2], W. M. U. DANIELS[3], M. V. MABANDLA[2]
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Abstract: Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder which accelerates cellular aging and precipitates neurodegenerative disease. While PTSD can accelerate aging and precipitate neurodegenerative disease, the underlying biological mechanisms are still unclear. In an effort to investigate the role of PTSD in the etiology of movement disorders, we assessed changes related to PTSD condition on the neurotrophic factors such as *transforming growth factor* beta-1 (*TGF*-β-1), glial cell-derived neurotrophic factor (GDNF), neurotrophin -3 (NT-3) and brain-derived neurotrophic factor (BDNF), D2 receptors, dopamine transporter (DAT) and Protein kinase B (AKT) in the striatum and cerebellum in a PTSD rat model. Adult rats were subjected to the Time-dependent sensitization (TDS), a PTSD animal model for 15 days. The conditional fear test was performed on day14. The elevated plus maze was used on day 18 and balance beam on day 19 to assess anxiety behavior and motor coordination. Corticotrophin-releasing factor (CRF), TGF beta-1, GDNF, BDNF, D2 receptors, DAT levels and AKT protein and gene expression were assessed using ELISA, Western blott, and Real-time qPCR. Our results show that the TDS resulted in an increase fear and anxiety - like behaviors. It showed an increased time spent to cross the beam, and an increased number of slips compared to the control. TDS increased CRF concentration. These effects were further observed, as in the striatum, NT-3 concentration, AKT protein expression and D2 receptors gene expression were increased, while DAT concentration was decreased. TGF beta-1, GDNF, DAT concentrations, AKT protein, GDNF and BDNF gene expressions were all decreased in the cerebellum. These effects suggest that the TDS leads to neurotropic factors changes, alterations of PKB/AKT- TGF-beta signaling and dopaminergic pathway in the striatum and the cerebellum, two structures involved in the pathophysiology of Movement disorders. These results suggest that PTSD increases the vulnerability of these structures to further insults later on in life, which might lead

to Movements disorders. Keywords: PTSD, BDNF, GDNF, TGF beta-1, DAT, AKT, striatum, cerebellum.

Disclosures: W.M.U. Daniels: None. **M.V. Mabandla:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

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Program#/Poster#: 165.06/RR19

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH1R15MH100689

Title: Early life trauma exposure yields resistance to fear extinction without increased anxiety in adulthood

Authors: *A. PEGUERO, E. J. PASCOE, K. M. SCHEIVE, J. J. QUINN, 45056
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Abstract: Early life stress exposure yields increased vulnerability for the development of posttraumatic stress disorder (PTSD) in adulthood. This has been modeled in rodents by showing that adult fear learning with mild to moderate aversive stimuli is enhanced in adulthood following early life stress exposure. In patients experiencing symptoms of PTSD, fear memory is resistant to extinction during exposure therapy, producing sustained exaggerated fear responses. However, these patients do not demonstrate symptoms of increased general anxiety. The present experiment addresses whether early life trauma exposure produces enhanced fear learning in adulthood (stress enhanced of fear learning; SEFL) that is resistant to extinction. In a separate experiment, we assessed whether an identical early life trauma experience yields increases in anxiety. Rats were exposed to zero or 15 footshocks on postnatal day 17 (PND17). In adulthood (approximately PND90), rats underwent fear conditioning in a novel context using 0, 1 or 3 footshocks. Rats were tested for enhanced fear learning and then subjected either to an additional 4 days of extinction training or anxiety testing using the elevated zero maze. On day 1 of extinction, trauma-exposed rats extinguished to control levels across the 10-minute session. However, on day 2 of extinction, trauma-exposed rats froze significantly higher than controls. Thus, within-session extinction looked comparable between trauma-exposed and control animals. However, between-session extinction was impaired in trauma-exposed rats. Trauma-exposed rats showed no differences in open quadrant entries, time spent, or distance traveled, or latency to first open quadrant entry compared to controls. These data provide additional strong construct validity for the SEFL model in the study of PTSD.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

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Topic: G.06. Post-traumatic Stress Disorder

Support: Collaborative Health Initiative Research Program (CHIRP) grant (308431-9.00-64532)

Title: Gene expression analysis in foot-shock induced PTSD model mouse

Authors: H. LI[1], *M. TANAKA[1], X. ZHANG[2], J. SINGH[2], C. DALGARD[2], M. WILKERSON[2], G. MUELLER[1], Y. ZHANG[1]
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Abstract: Posttraumatic stress disorder (PTSD) is developed by exposure to a threatening and/or horrifying event, and characterized by the presence of four major symptom clusters: anxiety, hyperarousal, avoidance, and sleep/wake cycle abnormality for a prolonged period of time. In order to investigate cellular and molecular alterations in CNS along with the development of PTSD symptoms, we constructed a PTSD-like rodent model by applying sequential electric foot shock (FS) (1.5 mA × 2 sec, 8 or 16 times) to male, 8-10 weeks old C57BL/6 mice. One to 5 weeks after FS, animals were examined by behavioral tests, and gene expression analyses in mouse brain were performed at 2, 5 and 7 weeks. Mice undergoing FS spent less time in the open zone or the center zone examined by elevated plus maze test or the open field test, indicating that the stressed mice acquired anxiety-like abnormality. The stressed animals showed higher arousal propensity demonstrated by the greater startle response to acoustic stimulus (120 dB × 40 msec). Those abnormal behaviors appeared after 1 week and continued for 5 weeks, while the behavioral changes were comparable between mice received 8 times and 16 times FS. Latency to move in the foot shock chamber or freezing time inside the chamber was significantly longer in stressed mice than control mice. Thus, those behavioral tests showed that our animal model acquired PTSD-like behavioral propensities. We then analyzed the gene expression in several brain regions including cingulate cortex, amygdala, and anterior hypothalamus. Using deep RNA sequencing (RNAseq), we identified more than 1000 genes in each region that were differentially expressed by DESeq2 R package, using unpaired two-class significance analysis and a false discovery rate threshold of 0.05. The most affected pathways include, but are not limited to, circadian entrainment, adrenergic signaling, MAPK signaling, calcium signaling, neurotrophin signaling, axon guidance, focal adhesion, RAS signaling and fatty acid biosynthesis. By real-time PCR, we validated the two process model genes involved in sleep regulation. We found *Crh* and *Crhr1* are significantly increased, while the expression of *Crhr2* is downregulated at 2 weeks after stress. These changes are correlated with the reduced expression of *Sstr2* and *Sstr5* and the increased expression of *Pou3f2*, suggesting the sleep-wake homeostasis is disturbed. The

expression of circadian entrainment genes (*Per 1, Per2, Cry1*, *Cry2*), glucocorticoid receptor *Nr3c1* and *Fos* is affected at 5-7 weeks after FS. These results suggest that control of CRH signaling might be critical for ameliorating sleep disturbances associated with PTSD.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

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Topic: G.06. Post-traumatic Stress Disorder

Support: NIAAA Intramural Research Program

NIH Grant AA018776

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Title: Identification and characterization of a genetic candidate for fear extinction from quantitative trait locus to pharmacology

Authors: *O. GUNDUZ CINAR[1], E. BROCKWAY[1], L. LEDERLE[1], T. WILCOX[2], L. R. HALLADAY[1], Y. DING[3], H. OH[4,5], E. F. BUSCH[1], K. KAUGARS[1], S. FLYNN[1], K. P. MACPHERSON[1], S. MASNEUF[1], C. PINARD[1], E. SIBILLE[4,5], E. J. CHESLER[2], A. HOLMES[1]
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Abstract: While stress and trauma are relatively common experiences, only some individuals develop anxiety disorders or trauma- and stressor-related conditions (aka post-traumatic stress disorder). Using a translational approach, we aim to identify gene candidates that would be critical in the extinction of traumatic memories and associated behaviors. For this in our previous studies we identified that inbred mice strain 129S1/SvImJ (S1) has impaired fear extinction compared to normally extinguishing C57BL/6J (B6) mice. First, we performed a quantitative trait loci (QTL) associated with fear extinction in a population generated from crossing these inbred mouse strains. Aim of the QTL was to identify phenotypic and genetic differences across mouse strains and to locate genomic regions associated with variation in trauma-relevant behaviors. Next, we performed BLA expression-profiling on genes located within an extinction-associated QTL and nominated *Ppid* (peptidylprolyl isomerase D, a member of the

tetratricopeptide repeat (TPR) protein family) as an extinction-related candidate gene. Subsequently, we showed that the extinction-impaired mouse strain had reduced BLA *Ppid* and *GR* (glucocorticoid receptor) gene expression, but retained the extinction-facilitating effects of a systemic GR agonist. Then, using a virus-based approach to directly regulate *Ppid* function, we demonstrated that downregulating BLA-*Ppid* was sufficient to impair extinction, while upregulating BLA-*Ppid* produced facilitation of extinction coupled to changes in *in vivo* neuronal extinction-encoding. Collectively, our results identify *Ppid* as a novel gene involved in regulating extinction possibly via modulations on downstream *GR* signaling. Identification of *Ppid* as a novel gene critically involved in fear extinction in mice could potentially help us to understand more on the genetic and pathophysiological mechanisms underlying risk for trauma-related disorders.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.09/RR22

Topic: G.06. Post-traumatic Stress Disorder

Title: Ganaxolone improves anxiety and PTSD associated behaviors in socially isolated mice by increasing allopregnanolone biosysnthesis

Authors: *M. S. SAPORITO[1], A. LOCCI[2], G. PINNA[3]
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Abstract: Ganaxolone (GNX, 3α-hydroxy-3β-methyl-5α-pregnan-20-one), a 3β-methylated synthetic analog of the GABAergic neurosteroid, allopregnanolone (Allo), improves anxiety-like and PTSD-like behaviors in mice. These improved behaviors include reduced aggression and reduced exaggerated contextual fear responses. GNX is a positive allosteric modulator of synaptic GABAA receptors (γ subunit containing receptors) and extrasynaptic GABAA receptors (δ subunit containing receptors), and this activity is considered to drive nearly all of the pharmacological activity of GNX. We hypothesized that GNX in addition to directly activating GABAA receptors, may elicit improved behavioral effects by elevating Allo biosynthesis and thereby further enhance GABAergic neurotransmission. In these studies, we used the socially isolated (SI) mouse, a validated preclinical model of PTSD, which shows downregulated Allo biosynthesis in association with dysfunctional behaviors. Neurosteroid levels were measured by

gas chromatography-mass spectrometry in the serum, frontal cortex, and striatum. GNX was given at doses (3.75-30 mg/kg, IP). These doses improve behaviors in SI mice but do not effect control, group-housed mice. While GNX failed to change Allo levels in the striatum and serum, the levels of Allo levels in the frontal cortex were doubled at these GNX doses. The GNX dose of 30 mg/kg induced a modest increase in the frontal cortex of Allo levels in group-house mice. This treatment also increased levels of pregnenolone, the precursor of all neurosteroids, suggesting that the mechanism of Allo increase is through GNX stimulation of upstream neurosteroid biosynthesis. The results from these studies indicate that GNX-induced elevation of cortical Allo levels may contribute to GNX-mediated improvements in behaviors

Disclosures: **M.S. Saporito:** A. Employment/Salary (full or part-time):; Marinus Pharmaceuticals. **A. Locci:** 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.; University of Illinois. **G. Pinna:** 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.; University of Illinois.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.10/RR23

Topic: G.06. Post-traumatic Stress Disorder

Support: TSNRP HU0001-16-1-TS16

CSTS

Title: Intravenous sub-anesthetic ketamine infusion dose-dependently enhances fear and delays fear extinction in male Sprague-Dawley rats

Authors: K. D. RADFORD[1], T. Y. PARK[2,3], L. OSBORNE-SMITH[1,4], *K. CHOI[2,3,1]
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Abstract: Trauma survivors diagnosed with post-traumatic stress disorder (PTSD) are haunted by dysfunctional fear memories that fail to extinguish, which leads to intrusive symptoms such as flashbacks, nightmares, and hyperarousal. Persistent fearful memories can last for months to decades following an event leading to increased psychological suffering and significant utilization of health care resources. Ketamine, a non-competitive glutamate antagonist at the N-

methyl-D-aspartate (NMDA) receptor, is gaining popularity as an off-label treatment for depression and PTSD patients resistant to traditional pharmacologic regimens. However, dose-dependent psychomimetic side-effects such as dissociation and hallucination raise concerns regarding the impact on psychological well-being and memory formation when administered in the peri-trauma period. There is a lack of pre-clinical literature that utilizes a clinically relevant intravenous (i.v.) ketamine infusion model in rodents. Therefore, we tested the effects of an extended sub-anesthetic i.v. ketamine infusion following rodent fear-conditioning (FC) on fear memory retrieval, extinction, and renewal. Rats received a single 2-h ketamine infusion (0, 1, 5, or 10 mg/kg/h) immediately after FC (3 tone and foot shock pairings). A separate cohort of animals received a 2-h ketamine infusion (0 or 5 mg/kg/h) 1 day after FC. Animals underwent two consecutive days of a cued extinction paradigm (exposure to auditory cue without foot shock) in a novel context. Contextual and cued fear renewal was measured in the FC chamber 1-day after final extinction testing. We found that an i.v. ketamine infusion administered immediately after FC dose-dependently enhanced fear memory retrieval, delayed extinction, and enhanced fear memory recall when tested over 4 days post-FC. Surprisingly, ketamine infusion (5 mg/kg/h) administered 1-day after FC exerted similar effects on fear memory retrieval, extinction, and renewal. Our results seem independent of a memory consolidation mechanism as timing of the extended ketamine infusion (immediate or 1-day later) produced similar delayed extinction and enhanced recall. In contrast to studies that utilized ketamine intra-peritoneal injections, a continuous i.v. ketamine infusion following FC exacerbated fear retrieval and impaired extinction. Further study is warranted to investigate the mechanisms of altered fear memory following the i.v. ketamine infusion route. Taken together, our findings suggest that a ketamine infusion administered in the peri-trauma period may exacerbate the dysfunctional fear extinction observed in stress related disorders.

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

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Topic: G.06. Post-traumatic Stress Disorder

Support: DoD award W81XWH-12-2-0048

Title: Increased mGluR5 and CB1R mRNA expression in the amygdala is associated with resilience to anxiety following predator odor exposure in rats

Authors: *J. SHALLCROSS, M. SCHWENDT, L. KNACKSTEDT
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Abstract: Post-traumatic stress disorder (PTSD) is a serious mental health condition that develops in a subset of individuals exposed to a trauma. To model PTSD in rodents, we exposed a large population of rats to 2,3,5-Trimethyl-3-thiazoline (TMT, a component of fox odor) once for 10 minutes and then tested for anxiety 7-21 days later using the elevated plus maze, acoustic startle response and freezing in the TMT context. We found that following a single exposure to TMT, subsets of both PTSD susceptible (PTSD) and PTSD "Resilient" animals emerge out of heterogeneous populations. Resilient animals show scores equivalent to non-TMT exposed controls in all anxiety tests while PTSD rats display high levels of anxiety. Three weeks following TMT or control exposure, quantitative PCR analysis indicated a significant upregulation of mGluR5 and CB1R mRNA in the amygdala of Resilient animals as compared to both control and PTSD groups. Using fluorescent in situ hybridization (FISH), we found that the concentration of mGluR5 mRNA expression was significantly higher in the basal lateral amygdala (BLA) of Resilient animals as compared to controls while concentration of mGluR5 mRNA expression in central amygdala did not differ among the groups. FISH analysis in the BLA also indicated increased co-expression of mGluR5 mRNA with glutamatergic marker vGlut1 mRNA in Resilient animals versus controls, however co-expression of mGluR5 mRNA and GABAergic marker GAD65 mRNA did not differ among the groups. Analysis of mGluR5 mRNA spots in individual cells that were either mGluR5/vGlut1 positive or mGluR5/GAD65 positive showed similar results, with higher numbers of mGluR5 mRNA spots in vGlut1 positive cells of Resilient animals, and no variance of mGluR5 mRNA in GAD65 positive cells between Resilient and controls. These results show that trauma resilience may be dependent on the amount of mGluR5 mRNA being expressed in glutamatergic BLA neurons. Supported by: DoD W81XWH-12-1-0048

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Poster

165. Animal Models of Trauma, Stress, and Anxiety I

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Program#/Poster#: 165.12/RR25

Topic: G.06. Post-traumatic Stress Disorder

Support: IRC Grant 1-19129

VT Sigma Xi Research Award 4-44130

Title: Interaction of regional distribution of NMDA receptor subtypes with glucocorticoid effects upon these subtypes as a potential substrate for PTSD

Authors: T. S. COTRONE, M. F. EHRICH, *B. G. KLEIN
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Abstract: Studies suggest intrusive fear memories in Post-Traumatic Stress Disorder (PTSD) may be more attributable to trauma-induced, pre-frontal cortex (PFC)-mediated dysfunction of fear extinction memory compared with amygdala (AMYG)-mediated dysfunction of fear memory formation. Other studies suggest a difference in representation of synaptic NR2A and NR2B NMDA receptor subtypes between AMYG and PFC/hippocampus (HIPPO). It was also reported that glucocorticoids (GC) may preferentially inhibit downstream effects of synaptic NR2A activation. Thus, we hypothesized that presence of GC, associated with trauma, preferentially exacerbates inhibition of fear extinction memory processes in PFC compared to conditioned fear memory processes in AMYG due to 1) differences between these regions in synaptic expression of NR2A and NR2B NMDA receptor subtypes and 2) differences in downstream effect of GC on these different subtypes. We employed the Single Prolonged Stress (SPS) protocol as a rat model of PTSD. 7 days after SPS or No SPS, rats were exposed to a light-cued fear conditioning paradigm, followed 24 and 48 hrs later by an extinction session. Rats were sacrificed after the 2nd extinction session and tissues removed from AMYG, PFC and HIPPO. For each region, 4 samples were prepared and respectively treated with a) bicuculline+vehicle, b) bicuculline+GC, c) bicuculline+NR2A blocker (NVP-AAM077), d) bicuculline+NR2B blocker (Ro-25-6981). Bicuculline was used to stimulate synaptic glutamate release in all samples and the phosphorylation of CREB (p-CREB) was used as an indirect measure of synaptic strength associated with memory formation. For No SPS rats, GC exposure produced a decrease in p-CREB in all 3 regions. The short latency of this decrease suggested a non-classical (non-gene transcription) mechanism of the effect. However, there was no difference in the magnitude of this decrease across regions. For No SPS rats, receptor blockers suggested representation of NR2A and NR2B subtypes in all 3 regions, but no representation difference across regions for NR2A or NR2B. This suggests, irrespective of whether GC preferentially inhibits downstream elements of synaptic NR2A activation, lack of differential representation of NR2A and NR2B across regions may underlie the similar effect of GC across regions in No SPS rats. SPS exposure changed the effect of receptor blockers in a manner suggesting reduction in NR2A representation in AMYG and a reduction in both NR2A and NR2B in the PFC. SPS exposure also appeared to diminish the GC-induced reduction in p-CREB that was seen in the PFC and HIPPO of No SPS rats. Support: IRC Grant 1-19129 and VT Sigma Xi Research Award 4-44130.

Disclosures: **T.S. Cotrone:** None. **M.F. Ehrich:** None. **B.G. Klein:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.13/RR26

Topic: G.06. Post-traumatic Stress Disorder

Support: DA031900

Title: Characterization of the neurobiological and behavioral correlates of susceptibility and resilience to traumatic stress

Authors: *E. M. BLACK[1], Z. D. BRODNIK[1], N. W. SNYDER[2], R. A. ESPAÑA[1]
[1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]A.J. Drexel Autism Inst., Philadelphia, PA

Abstract: Patients with posttraumatic stress disorder (PTSD) display symptoms such as hypervigilance and increased anxiety, as well as increased comorbidity with substance use disorder. Though many individuals are exposed to traumatic stress, only approximately 30% develop PTSD ("susceptible") while the other 70% demonstrate resilience to the stress ("resilient"). We used exposure to a predator odor to model PTSD in rats. To mimic the divergent responses to traumatic stress observed in the human population, we segregated subjects as susceptible or resilient based on elevated plus maze and context avoidance behaviors. We then examined behavioral and neurochemical differences across susceptible, resilient, and control groups in order to develop profiles of these heterogeneous populations. We examined various PTSD-related symptoms, measuring hypervigilance with acoustic startle response, anhedonia with sucrose preference tests, and locomotor response to cocaine with open-field activity. In addition to differences on these behavioral tasks, susceptibles and resilients also displayed differences in corticosterone levels, suggesting differing physiological responses to stress. Further, using microdialysis, we observed alterations in dopamine signaling between the two groups. Our data suggest that these subjects have distinct neurobiological profiles following traumatic stress, with susceptibles displaying behavioral and neurochemical elevations in anxiety-related systems. This research elucidates the differences between susceptibles and resilients, providing compelling information that may lead to the development of more targeted treatments for individuals with PTSD.

Disclosures: E.M. Black: None. **Z.D. Brodnik:** None. **N.W. Snyder:** None. **R.A. España:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.14/RR27

Topic: G.06. Post-traumatic Stress Disorder

Support: NRF-2017R1A2B4012237

NRF-2015M3C7A1031395

Title: Target gene prediction of differentially expressed small RNAs in the prefrontal cortex of FKBP5 knock out mouse

Authors: *K. CHOI, S. SIHWAN, K. HYO JUNG
Chung-Ang Univ., Seoul, Korea, Republic of

Abstract: Posttraumatic Stress Disorder (PTSD) is one of the most prevalent and debilitating psychiatric disorder. Since the hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the regulation of stress responses, it has been implicated in the etiology of stress related disorders such as PTSD. In addition, glucocorticoid receptor (GR) hypersensitivity has been described to be one of the endocrine hallmarks of PTSD. FK506-binding protein 51 (FKBP5) is a co-chaperone of HSP90 in the GR molecular complex and a key regulator of the sensitivity of GR. In this study, we examined the differential expression of miRNAs in the prefrontal cortex of FKBP5 KO mice brain compared to the WT by next-generation sequencing approaches. As a result, we identified 37 of differentially expressed miRNAs in the FKBP5 KO mice. We also performed prediction of miRNA targets using several online software tools such as miRDB, miRanda and TargetScan. Target gene prediction suggested that the differentially expressed miRNAs in the brain of FKBP5 KO mice may be involved in focal adhesion pathway, chromatin modification, neurodevelopment, cell migration and axon guidance. The expression of predicted target gene was confirmed in the prefrontal cortex of FKBP5 mice brain by quantitative real-time PCR. These results will provide further understanding of the pathophysiology of PTSD.

Disclosures: K. Choi: None. **S. Sihwan:** None. **K. Hyo Jung:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.15/RR28

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH/NIDA DA017949

Temple Univeristy CARAS grant

Title: Sex-dependent effects of chronic nicotine in spontaneous recovery of contextual fear

Authors: *J. TUMOLO[1], M. G. KUTLU[2], T. J. GOULD[3]
[1]Psychology, Temple Univ., Philadelphia, PA; [2]Penn State Univ., University Park, PA; [3]Biobehavioral Hlth., Penn State, University Park, PA

Abstract: Post-traumatic stress disorder and nicotine use are highly correlated with 45.3% of the clinical population smoking versus 22.5% of the healthy population. Previous studies from our

lab showed that chronic nicotine impaired fear extinction and acute nicotine enhanced spontaneous recovery of contextual fear in adult male mice. We investigated if chronic nicotine administration altered spontaneous recovery (SR) or recall of contextual fear in adult male and female C57BL6/J mice. Spontaneous recovery subjects were trained and tested in contextual fear conditioning, given five extinction sessions, and were either implanted with mini-osmotic pumps containing 12.6 mg/kg nicotine or underwent sham surgery. Recall subjects were also trained and tested in contextual fear, did not undergo extinction, and were either implanted with mini-osmotic pumps or given sham surgeries. One week following surgery, subjects were tested for SR and recall. Our results showed that chronic nicotine significantly enhanced SR in female mice and decreased SR in males. Chronic nicotine had no effect on recall of contextual fear in males or females. Female sham mice also had less baseline SR than male sham mice. Overall, these results show that chronic nicotine administration has a differential effect on SR of contextual fear depending on sex, that female mice are less likely to experience SR without the drug, and that nicotine has no effect on recall of contextual fear.

Disclosures: **J. Tumolo:** None. **M.G. Kutlu:** None. **T.J. Gould:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.16/RR29

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant 1P20GM103653

University of Delaware Research Foundation

Title: Single prolonged stress causes changes in neural activation within the PAG and Amygdala during fear conditioning

Authors: R. DELLA VALLE, E. MOULTON, M. CHAMNESS, *D. K. KNOX
Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Single prolonged stress (SPS) refers to series of heterogeneous stressors (e.g. two hour restraint, twenty minute forced swim, and ether exposure until anesthetized) applied over a three hour window. SPS induces symptoms that resemble PTSD and is often used as a model of traumatic stress. SPS exposure leads to retention deficits in extinction of fear learning, but whether this is due to deficits in extinction memory or changes in fear memory is currently unknown. One possibility is that, after SPS, fear memories become more persistent, leading to deficits in the expression of extinction memory. Previous work in our lab has established differences in immediate early gene activity (c-Fos and c-Jun, two dimers of the AP-1

transcription factor) in extinction circuitry after extinction training and testing in SPS-exposed rats. Using c-Fos and c-Jun to measure neural activity revealed more about neural circuits through which SPS leads to extinction retention deficits than using c-Fos or c-Jun alone. However, the neural circuitry through which SPS-induced changes in fear memory could lead to extinction retention deficits have not been investigated. In order to address this, rats were exposed to either SPS or control stress. Rats then underwent either cued fear conditioning or tone exposure in the absence of shock. C-Fos and c-Jun were then assayed in sub regions of the medial prefrontal cortex (mPFC), lateral (LA), basal (BA) and central (CeA) nuclei of the amygdala, dorsal and ventral hippocampus, and periaqueductal gray (PAG). Preliminary analysis suggests that neural activity in the CeA, LA, and BA is sensitized in SPS rats as expression of c-Jun was enhanced in SPS rats during fear conditioning and tone exposure. C-Fos and c-Jun co-varied in sub regions of the PAG, with decreases in c-Jun in SPS rats during fear conditioning in the dorsomedial PAG and increases in c-fos in SPS rats in the ventral PAG after fear conditioning. These preliminary findings suggest that SPS alters neural activity in fear circuitry with changes in neural activity in the PAG being fear learning specific and changes in neural activity in the amygdala being fear learning non-specific. Continuing experiments are examining functional connectivity patterns among the PAG and amygdala during fear conditioning, extinction training, and extinction testing, as well as c-Fos and c-Jun expression in GABAergic neurons in the CeA and PAG during fear and extinction learning/memory.

Disclosures: R. Della Valle: None. **E. Moulton:** None. **M. Chamness:** None. **D.K. Knox:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.17/RR30

Topic: G.06. Post-traumatic Stress Disorder

Support: NIH Grant R01MH103848

Title: Characterization of novel mouse model reveals a new role for FKBP5 in regulating synaptic plasticity

Authors: *L. J. BLAIR[1], M. CRIADO-MARRERO[2], X. WANG[3], D. ZHENG[4], J. M. WEBSTER[2], E. J. WEEBER[5], C. A. DICKEY[6]
[1]Mol. Med., USF Byrd Inst., Tampa, FL; [2]Mol. Med., [4]Dept. of Mol. Med., [5]Mol Pharmacol & Phys, [6]Mol. Med./Byrd Inst., [3]Univ. of South Florida, Tampa, FL

Abstract: Single nucleotide polymorphisms (SNPs) in FK506-binding protein 5 (FKBP5) have been shown to combine with environmental factors increases risk for psychiatric diseases, like

post-traumatic stress disorder (PTSD). While mechanisms of FKBP5 contribution to this increased risk are still under investigation, it has been shown that many of these SNPs increase FKBP5 expression through decreased FKBP5 DNA methylation. To evaluate the consequences of this enhanced expression, we generated a novel mouse model using targeted insertion of a single copy of the *FKBP5* gene at the Hipp11 locus. The inserted FKBP5 contained a tetracycline operator, which allowed for high expression throughout the forebrain when crossed with an activator line. Evaluation of this model was done using behavioral, electrophysiological, and biochemical analysis. Overall, we have found that high expression of FKBP5 alters memory as tested by both Morris water maze and long-term depression. Importantly, this alteration was detectable in the absence of stress and other environmental factors. Further studies in this model may help reveal additional mechanisms by which FKBP5 alters learning and memory.

Disclosures: **L.J. Blair:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pending Patent on rTgFKBP5 transgenic mouse. **M. Criado-Marrero:** None. **X. Wang:** None. **D. Zheng:** None. **J.M. Webster:** None. **E.J. Weeber:** None. **C.A. Dickey:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.18/RR31

Topic: G.06. Post-traumatic Stress Disorder

Support: Davee Foundation

NIH DA-037844

Title: Genetic model of co-morbid posttraumatic stress disorder and increased alcohol intake

Authors: *E. REDEI[1], P. H. LIM[1], G. SHI[2], T. WANG[2], M. MULLIGAN[2], H. CHEN[2]
[1]Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Dept Pharmacol, Univ. Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Posttraumatic stress disorder (PTSD) is a highly debilitating mental disease and is often comorbid with alcohol use disorder and depression. Several animal models have been established to study the persistence of fear memory after stress in PTSD. However, its comorbidity with other disorders has been more difficult to model. Here we demonstrate the comorbidity of stress-enhanced fear memory, a model of PTSD, and increased alcohol intake in a genetic animal model of depression. Selective breeding of the Wistar Kyoto rat for high and low immobility in the forced swim test led to the more immobile (WMI) and less immobile (WLI) inbred strains after >35 generations, where the WMI is a genetic model for depression. Stress-

enhanced fear memory was tested in adult WMI and WLI rats by first exposing them to a 2-hour restraint stress, while the controls were not stressed. Two days later, rats were placed into a fear conditioning chamber for 3 min of habituation, followed by three mild shocks (0.8mA, 1 s each) over 3 min. Contextual fear memory retrieval was measured 24 h later. Male WMIs showed greatly exaggerated fear memory, indicated by more freezing, after stress, while WLIs did not. In contrast, WLI females demonstrated increased fear memory compared to WMI females. In parallel with PTSD symptom characteristics in women, WMI females exposed to stress prior to fear conditioning showed an enhanced activity profile by rearing more before and after the shock. A second group of naive rats was trained to self-administer alcohol using licking as the operant response. Licking on the active spout meeting a variable ratio 10 schedule resulted in the delivery of 60µl 6.5% alcohol with a 20s-timeout period while licking on the inactive spout had no programmed consequence. Both WMI and WLI rats emitted a significantly greater number of licks on the active than on the inactive spout. The number of active licks also increased significantly across training. The WMI rats consumed significantly more alcohol (0.50 ± 0.02 g/kg) than the WLI (0.37 ± 0.02 g/kg) rats and no sex difference was found. Together, these data demonstrated that the WMI is a novel genetic model suitable to study the comorbidity of PTSD and alcohol abuse disorder.

Disclosures: E. Redei: None. **P.H. Lim:** None. **G. Shi:** None. **T. Wang:** None. **M. Mulligan:** None. **H. Chen:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.19/RR32

Topic: G.06. Post-traumatic Stress Disorder

Support: DOD Award W81XWH-15-1-0521 (GP)

Title: Stimulation of the endocannabinoid system by PEA engages neurosteroid biosynthesis to improve anxiety and fear in a PTSD mouse model

Authors: A. LOCCI[1], *G. PINNA[2]
[1]The Psychiatric Institute, UIC, Chicago, IL; [2]Univ. of Illinois At Chicago, Chicago, IL

Abstract: Post-traumatic stress disorder (PTSD) is a debilitating condition that affects 8-13% of the general population and 1 in 5 war veterans. There is no specific treatment available and current medication only helps 50% of patients who show a high relapse rate. The corticolimbic levels of the $GABA_A$ receptor-active, neurosteroid, allopregnanolone are downregulated in socially isolated (SI) mice, a mouse model of PTSD, and low non-serotonergic doses of fluoxetine normalize its brain levels and improves behavior. The endocannabinoid (eCB) system

regulates emotions and stress responses and new cannabinoid ligands have become a major focus for anxiety and PTSD treatment. Disruption of the eCB system enhances fear acquisition and impairs fear extinction while activation of peroxisome proliferator-activated receptor (PPAR)-alpha by the endocannabinoid, N-palmitoylethanolamine (PEA), induces antidepressant effects comparable to those elicited by FLX. Like FLX, PEA induces allopregnanolone biosynthesis in cell cultures and brain stem. Thus, these findings suggest that PEA may also induce allopregnanolone biosynthesis in corticolimbic areas and thereby improve anxiety and fear responses. Our results show that PEA induced a significant dose-dependent (5-20 mg/kg) increase of allopregnanolone levels in the hippocampus, amygdala and olfactory bulb of SI mice and in the frontal cortex at the dose of 20 mg/kg. The same treatment did not modify allopregnanolone levels in the striatum or in group-housed mice. PEA, by a reconsolidation blockade, facilitated fear extinction and also prevented the spontaneous recovery of fear memory after passage of time in SI mice. Furthermore, PEA induced a marked anxiolytic and antiaggressive effect, which was mimicked by the PPAR-alpha agonist, GW7647, prevented by GW6471, a potent PPAR-alpha inhibitor, and abolished in PPAR-alpha KO mice. Locomotor activity was not altered by these treatments. Our results show that PPAR-alpha regulates emotions and mood by engaging neurosteroid biosynthesis, which may offer a novel target in PTSD therapy.

Disclosures: **A. Locci:** None. **G. Pinna:** None.

Poster

165. Animal Models of Trauma, Stress, and Anxiety I

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 165.20/RR33

Topic: G.06. Post-traumatic Stress Disorder

Support: MH-097988 to SEH, DJT, VM

Title: Prior stress differentially alters anxiety-like responding to intra-BNST pituitary adenylate cyclase activating polypeptide (PACAP) in male and female rats

Authors: *S. B. KING[1], D. J. TOUFEXIS[1], V. MAY[2], S. E. HAMMACK[1]
[1]Psychological Sci., [2]Neurolog. Sci., Univ. of Vermont, Burlington, VT

Abstract: Repeated exposure to stressful stimuli can result in psychopathologies that are more common in women, including anxiety disorders and trauma-related disorders. Moreover, altered peptide expression in anxiety-related brain structures such as the bed nucleus of the stria terminalis (BNST) has been implicated in these disorders. In male rodents, chronic variate stress (CVS) has been shown to increase BNST pituitary adenylate cyclase activating polypeptide (PACAP) and its cognate PAC1 receptor transcript, and BNST PACAP signaling may mediate

the maladaptive changes associated with chronic stress. Furthermore, recent evidence suggest that PACAP may interact with ovarian hormones (i.e., estrogen) to contribute to sex differences in stress-related disorders. Here, we examined whether chronic variate stress (CVS) would sensitize the behavioral and/or endocrine response to a subthreshold BNST PACAP infusion. Male and cycling female rats were exposed to a 7 day CVS paradigm previously shown to upregulate BNST PAC1 receptor transcripts; control rats were not stressed. 24 hr following the last stressor, rats were bilaterally infused into the BNST with 0.5 µg PACAP. We found an increase in startle and plasma corticosterone levels 30 minutes following intra-BNST PACAP infusion in male rats that had been previously exposed to CVS. In cycling females, CVS attenuated the startle response to intra-BNST PACAP. Unstressed females showed enhanced startle similar to what was observed in males. The effects in females appeared to be dependent on estrus. These results suggest that the level of stress and circulating ovarian hormones may differentially regulate the PACAPergic system in males and females to influence anxiety-like behavior and may be one mechanism underlying the discrepancies in human psychiatric disorders.

Disclosures: S.B. King: None. **D.J. Toufexis:** None. **V. May:** None. **S.E. Hammack:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.01/RR34

Topic: H.01. Animal Cognition and Behavior

Title: Projection-specific inactivations of prelimbic cortex to the nucleus reuniens of the thalamus and perirhinal/lateral entorhinal cortex impairs memory for sequences of events in rats

Authors: *M. JAYACHANDRAN[1], M. SCHLECHT[2], S. B. LINLEY[3], R. P. VERTES[4], T. A. ALLEN[1]
[1]Dept. of Psychology, [2]Psychology, Florida Intl. Univ., Miami, FL; [3]Florida Atlantic Univ., Boca Raton, FL; [4]FAU/Ctr Complex Systems, Boca Raton, FL

Abstract: Episodic memory includes memory for order of events as they occurred during an experience. Accumulating evidence suggests that this capacity depends on a network of structures including the hippocampus (HC) and the medial prefrontal cortex (mPFC). However, little is known about the specific circuit pathways between HC and mPFC that are critical to sequence memory. Although HC has direct projections to mPFC, no direct return projections exist. Notably, mPFC projects to both thalamic and cortical intermediaries in route to HC. Here, we examined the role of mPFC to HC pathways, specifically prelimbic cortex (PL) projections, in memory for sequences of events. We focused on PL projections to the nucleus reuniens of the thalamus (RE) and to perirhinal and lateral entorhinal cortex (PER/LEC). We hypothesize that

(1) PL is essential to memory for sequence of events, and (2) direct projections from PL to RE, and PL to PER/LEC are also critical to memory for sequence of events reflecting the necessity of multiple communications pathways in sequence memory. Temporary inactivations of PL, PL-to-RE, and PL-to-PER/LEC was achieved using a virally-delivered hM4Di DREADD (AAV9.CAG.mCherry-2a-hM4d$_{nrxn}$.WPRE.SV40) delivered to PL and coupled with cannula targeting RE and PER/LEC. hM4Di$_{nrxn}$ can be used in conjunction with cannula to deliver clozapine N-oxide (CNO) locally and limit inactivation to specific projection terminals. Rats were trained on a non-spatial sequence task in which they demonstrated memory for two odor sequences (Seq1: A_1-B_1-C_1-D_1 and Seq2: A_2-B_2-C_2-D_2) located at opposite ends of a linear track. Rats demonstrated sequence memory by holding in the nose poke for 1s for in-sequence (InSeq) odors, and withdrawing prior to 1s for out of sequence (OutSeq) odors. Rats were water restricted and received a small water reward for correct responses on both InSeq and OutSeq trials. We found that intraperitoneal CNO injections (1mg/kg; 1mg/mL), used to inactivate PL neurons themselves, significantly impaired sequence memory, consistent with previous findings using muscimol. A detailed histologic analysis of hM4Di expressing PL neurons revealed these cells project to several structures in the thalamus and cortex. Thus, the downstream structures that require PL afferent activity for sequence memory remains unclear. Projection-specific inactivation of PL-to-RE and PL-to-PER/LEC with CNO (0.5 uL; 1ug/uL) also significantly impaired sequence memory. These results demonstrate that PL projections to both RE and PER/LEC are critical in memory for sequences of events, highlighting a role for top down mPFC to HC projections in this form of memory.

Disclosures: M. Jayachandran: None. **M. Schlecht:** None. **S.B. Linley:** None. **R.P. Vertes:** None. **T.A. Allen:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.02/RR35

Topic: H.01. Animal Cognition and Behavior

Title: NeuroCap: A 3D-printable stereotaxic system for fast, precise, and reliable chronic brain implants in rodents

Authors: *L. M. ALLEN, M. JAYACHANDRAN, T. A. ALLEN
Psychology Dept, Florida Intl. Univ., Miami, FL

Abstract: The NeuroCap brain implantation system is a 3D-printable stereotaxic device for neurosurgery in rodents that is easily modified in CAD software (e.g., Autodesk Inventor) for specific applications. The system is composed of four primary components: (1) NeuroCap, (2) the Implant Jig, (3) the Surgical Stencil, and (4) the Protective Cap. Each component serves a

unique function, and can be used together, or separately depending on the application. The NeuroCap System increases surgical speed, accuracy, and reliability. The surgeries can be conducted in the absence of ear bars because of the surgical stencil which has cross-hair assisted alignment holes at bregma and lambda. The ear bar-free approach reduces both the time of the surgery (e.g., ~45min start to finish for six-pole cannula implant) and seems to reduce post-surgical recovery times. Here, we demonstrate feasibility using the NeuroCap system in lieu of a traditional U-frame stereotaxic apparatus and manipulator arm in cannula implantations of prelimbic cortex (PrL), dorsal hippocampus (dHC), and ventral hippocampus (vHC), as well as a 16-wire array of electrodes implanted in PrL. Rats implanted with the NeuroCap device for cannula had replicable, precise, and symmetrical placements comparable to those achieved by traditional U-frame stereotaxic devices. The implants were sturdy and well-protected due to the Protective Cap. Rats implanted with the 16-wire array had stable single-unit activity over many weeks, and were able to freely perform our sequence memory and interval timing tasks that use repeated nose pokes as a daily behavior response. We have also developed versions of NeuroCap to implant driveable tetrodes as well as a device for singular injections in the absence of a stereotactic manipulator arm (e.g. DREADDs, AAVs, excitotoxins, etc.). Notably, our 3D files can be shared and duplicated with ease, and are inexpensive supporting goals of open science in experimental brain surgeries. In conclusion, the NeuroCap system has been adapted to multiple experimental paradigms in our lab, and should be a useful for rodent brain surgery across neuroscience research.

Disclosures: **L.M. Allen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder. **M. Jayachandran:** None. **T.A. Allen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent Holder.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.03/RR36

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH0995902

Title: The effect of chemogenetic inactivation of the nucleus reuniens (RE) or selective RE terminals to the hippocampus or medial prefrontal cortex on spatial working memory in a delayed nonmatch to sample t-maze task in rats

Authors: ***T. D. VIENA**[1], M. E. SCHREIBER, 33431[1], K. J. HARRIS[1], T. A. ALLEN[2], S. B. LINLEY[1], R. P. VERTES[1]

[1]Ctr. for Complex Systems and Brain Sci., Florida Atlantic Univ., Boca Raton, FL; [2]Dept. of Psychology, Florida Intl. Univ., Miami, FL

Abstract: Spatial working memory (SWM) relies upon the interactions of the hippocampus (HF) and medial prefrontal cortex (mPFC). The nucleus reuniens (RE) of the midline thalamus represents an anatomical node in HF-mPFC circuitry, allowing for the bidirectional flow of information across these structures. Additionally, several reports have found RE is instrumental in both spatial and nonspatial working memory tasks that recruit both the HF and mPFC (for review see Griffin 2015; Vertes et al., 2015). However, little is known regarding how RE acts to transfer information through this circuit. There are strong bilateral connections between RE and CA1/subiculum of the ventral hippocampus (vHF). While RE and the vHF densely innervate the mPFC, there are no return projections of mPFC to the hippocampus, which suggests RE completes this anatomical loop. Despite this, most studies have concentrated on a dorsal hippocampal (dHF) and mPFC network governing spatial behavior. In the absence of direct dHF to mPFC projections, RE may also serve as a link between the dHF and mPFC. In the present study, we used a chemogenetic approach to selectively inactivate RE and RE specific projections to the dHF, vHF, or mPFC to disrupt specific RE terminal sites during spatial working memory. Long Evans rats, which virally expressed the hM4Di DREADD (designer receptor exclusively activated by a designer drug) inhibitory receptor in RE, were implanted with chronic bilateral cannulas targeted for vHF and mPFC or dHF and mPFC. Rats were tested on a delayed nonmatch to sample spatial alternation working memory task, wherein they were required to retain spatially relevant information at delays of 30 and 120 seconds. Clozapine-n-oxide (CNO) delivered i.p. produced neuronal inhibition of virally infected cells in RE and impaired spatial working at doses of 5mg/kg in comparison to vehicle control (phosphate buffered saline), $F(2,9)= 5.50$, $p < 0.05$. By contrast, local infusions of CNO were used to selectively inhibit RE terminals projecting to target sites. Our findings indicate that selectively inhibiting RE fibers distributing to the mPFC impaired SWM, but selectively inhibiting RE terminals projecting to the vHF produced no significant effect. The results of this study further support the role for RE as a critical link in the transfer of mnemonic information between the HF and mPFC. Moreover, it suggests that cognitive deficits seen in schizophrenia and other neurological disorders may result from dysregulation of this established circuit between the hippocampus, nucleus reuniens and the medial prefrontal cortex.

Disclosures: **T.D. Viena:** None. **M.E. Schreiber:** None. **K.J. Harris:** None. **T.A. Allen:** None. **S.B. Linley:** None. **R.P. Vertes:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.04/SS1

Topic: H.01. Animal Cognition and Behavior

Title: Inactivation of the nucleus reuniens of the thalamus through hM4Di DREADDs improves interval timing performance

Authors: *A. DRAPER[1], M. JAYACHANDRAN[2], S. B. LINLEY[3], R. P. VERTES[4], T. A. ALLEN[2]
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Abstract: Timing abilities are critical to memory and behavior, and are dysfunctional in several disorders such as Alzheimer's disease, schizophrenia, and attention-deficit and hyperactivity disorder. Prominent research has shown that interval timing depends on corticostriatal circuits, but less work has focused on medial temporal lobe circuitry which is also critical in various timing tasks. Notably, the medial temporal lobe system and corticostriatal system potentially interact through a common convergence in the medial prefrontal cortex. In relation, the nucleus reuniens of the thalamus (RE) serves as a link between the hippocampus and the medial prefrontal cortex. However, little is known about the role of RE in interval timing. Here we investigated the role of RE in interval timing using a bi-peak fixed-interval procedure. Briefly, water restricted rats received a small water reward after a nose poke at 10s (25% of trials) or 40s (75% of trials) following the onset of white noise. Rewarded pokes terminated trials. After a 2 -3 weeks of daily training sessions rats poking behavior increases in frequency near 10s and near 40s peaks. Rats were given virally-delivered hM4Di DREADDs (AAV9.CAG.mCherry-2a-hM4d$_{nrxn}$.WPRE.SV40) targeting RE, mediodorsal nucleus of the thalamus (MD), or dorsal medial striatum. Rats were also implanted with cannula targeting prelimbic cortex (PL) in both RE and MD groups for projection-specific manipulations. Notably, hM4Di$_{nrxn}$ can be used in conjunction with cannula to deliver clozapine N-oxide (CNO) locally and limit inactivation to specific projection terminals. We found that CNO delivered i.p. in RE, or locally delivered to inactivate RE-to-PL projections, caused a decrease in early responses which was coupled with a reduction in variance at the 10s and 40s intervals. In contrast, we found that CNO delivered i.p. in rats with hM4Di expression in dorsal medial striatum or MD, or CNO delivered locally to inactivate MD-to-PL projections, caused an increase in early responses which was coupled with an increase in variance at the 10s and 40s intervals. Taken together, these results suggest improved interval timing performance following a reduction in RE-to-PL activity, and impaired interval timing performance following reductions to MD-to-PL activity.

Disclosures: A. Draper: None. **M. Jayachandran:** None. **S.B. Linley:** None. **R.P. Vertes:** None. **T.A. Allen:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.05/SS2

Topic: H.01. Animal Cognition and Behavior

Title: Role of the thalamic nucleus reuniens in hippocampo-cortical coupling

Authors: *M. FERRARIS, A. GHESTEM, A. F. VICENTE, C. BERNARD, P. P. QUILICHINI
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Abstract: The hippocampus (HPC) and medial prefrontal cortex (mPFC) have well-established roles in memory encoding and retrieval. How HPC and mPFC exchange information is not fully understood. The midline thalamic nucleus reuniens (RE) is bidirectionally structurally connected to both HPC and mPFC. The RE thus seems ideally posed to regulate hippocampo-cortical interactions and coordinate their functions. Whether the RE insures such regulation or coordination is unknown. In order to test this hypothesis, we have recorded simultaneously unit activities and local field potentials in the three structures during two stable brain states: theta and slow oscillations in anesthetized rats, which mimic REM sleep and slow wave sleep, respectively. Our results show that during the slow-oscillations state, mPFC and HPC displayed coordinated gamma bursts that entrain some of the local neuronal population. This HPC-mPFC gamma synchronization is also present during slow-wave sleep in non-anesthetized rats. A large portion of RE neurons increased their firing probability prior the onset of these gamma bursts. We propose that the specific activity of these neurons could coordinate gamma bursts between the HPC and mPFC. Preliminary results of RE inactivation experiments support this proposal. Thus, RE neurons may be involved in HPC-mPFC gamma synchronization, making the RE as a potential functional hub for regulating hippocampo-cortical coupling.

Disclosures: M. Ferraris: None. **A. Ghestem:** None. **A.F. Vicente:** None. **C. Bernard:** None. **P.P. Quilichini:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.06/SS3

Topic: H.01. Animal Cognition and Behavior

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Sloan Foundation Fellowship

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HHMI

Title: Hippocampal-prefrontal reactivation during awake and sleep sharp-wave ripple events

Authors: *W. TANG[1], J. D. SHIN[1], L. M. FRANK[3], S. P. JADHAV[2]
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Abstract: Coordinated reactivation in the hippocampal-prefrontal (PFC) network during sharp-wave ripple (SWR) events is thought to play a role in learning and memory-guided behavior. We and others have shown that SWRs during both behavior (awake SWRs) and slow-wave sleep (sleep SWRs) contribute to spatial learning, and both engage PFC activity during reactivation (*Girardeau et al., 2010; Wierzynski et al., 2010; Jadhav et al., 2012, 2016*). The relationship between these two forms of reactivation is not yet known, however, and whether they have any different properties or serve different roles in memory processes, is still unclear. To address this question, we recorded neural ensembles simultaneously in PFC and CA1 across sleep and behavior sessions as rats (n = 5) learned a W-track spatial alternation task (*Jadhav et al., 2016*). We previously showed that awake PFC reactivation comprises both excitation of task-related content and inhibition of neurons that are more active during immobility. Surprisingly, we found that PFC modulation during awake SWRs is only weakly correlated with that seen during slow-wave sleep. These differences are manifested in multiple ways. First, PFC neurons are primarily excited during sleep SWRs, with some awake SWR-inhibited cells showing significant excitation during post-task sleep SWRs. We also found overall higher SWR co-firing for awake as compared to sleep SWRs, suggesting better coordination of CA1-PFC activity in the waking state. Indeed, we found awake SWRs reactivated spatial experiences in the CA1-PFC network with higher fidelity than sleep SWRs, similar to intra-hippocampal reactivation (*Karlsson and Frank, 2009*). The SWR co-firing of CA1-PFC pairs is significantly correlated to their spatial representation similarity (i.e., spatial correlation) in both waking and post-task sleep stages, but this association is stronger during awake SWRs. CA1-PFC ensemble reactivation, quantified using reactivation strength and explained variance (*Peyrache et al., 2009; Kudrimoti et al., 1999*), is also significantly stronger during awake SWRs. Finally, CA1-PFC spatial reactivation is strongest during initial learning in a novel environment, especially for awake SWRs. We thus found a more precise recapitulation of behavioral representations and more structured

reactivation in the CA1-PFC network for awake SWRs as compared to sleep SWRs, which is especially enhanced during initial learning. These findings support the idea that awake reactivation subserves memory functions related to current behavior, whereas sleep reactivation may play a more complex role, such as integrating experiences across multiple episodes.

Disclosures: W. Tang: None. **J.D. Shin:** None. **L.M. Frank:** None. **S.P. Jadhav:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.07/SS4

Topic: H.01. Animal Cognition and Behavior

Support: ONR MURI Grant N000141310672

Title: Effects of learning on the co-occurrence of hippocampal sharp-wave ripples and prefrontal cortical spindles in the rat

Authors: *B. HARPER[1], M. CONTRERAS[1], J.-M. FELLOUS[2]
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Abstract: The synaptic modifications resulting from the co-occurrence of hippocampal sharp-wave ripple oscillations (100-250 Hz) and cortical spindle oscillations (12-15 Hz) are thought to be a key mechanism for memory consolidation. Learning is known to increase ripple density in the hippocampus and spindle density in the medial prefrontal cortex (mPFC) during subsequent sleep. We record simultaneously from dorsal hippocampal area CA1 and from the prelimbic cortex in mPFC in adult male Brown Norway rats to test the hypothesis that learning-related increases in oscillation density enhance the cross-correlation between ripples and spindles. We first confirm that ripple and spindle density increase during sleep after learning in a spatial navigation task on an open field maze. Same-day recordings after learning and non-learning tasks show no significant enhancement of ripple-spindle cross-correlation during post-task sleep. Neither the percentage of spindles with at least one co-occurring ripple, nor the percentage of ripples during or near spindles, seems to be modulated by the tasks. However, comparison with shuffled data shows that ripples may occur before, during, or after spindles at rates greater than chance. We suggest that the statistics of ripple and spindle co-occurrence may be fixed, and that higher oscillation densities may enhance memory consolidation after learning by concomitantly increasing the cellular and synaptic interactions occurring during these oscillations. We explore pharmacological means of changing the sleep architecture and the statistics of ripple-spindle co-occurrence. This study extends previous findings on hippocampo-cortical coordination and offers a new perspective on the systems-level mechanisms of memory consolidation.

Disclosures: **B. Harper:** None. **M. Contreras:** None. **J. Fellous:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.08/SS5

Topic: H.01. Animal Cognition and Behavior

Support: CIHR (MOP 130393)

Title: Prefrontal cortical disinhibition induces widespread neuronal activation in cortical and subcortical structures that are modified by spatial learning

Authors: *M. AUGER[1], J. MECCIA[2], L. A. GALEA[3], S. B. FLORESCO[4]
[1]Dept Psychology, [2]Psychology, [3]Djavad Mowafaghian Ctr. from Brain Health, Psychology, Univ. of British Columbia, Vancouver, BC, Canada; [4]Univ. British Columbia, Vancouver, BC, Canada

Abstract: Deficient prefrontal GABA function is hypothesized to play a role in altered cognition observed in schizophrenia. We and others have found that pharmacological reduction of prefrontal cortex (PFC) $GABA_A$ receptor activity recapitulates many cognitive and behavioral features of schizophrenia, including impaired spatial memory. Intriguingly, these treatments can disrupt performance of cognitive tasks not normally dependent on the PFC, including the reference/working memory (RM/WM) variant of the radial maze. One explanation for this is that PFC disinhibition may cause aberrant increases in neuronal activation in PFC efferent regions. To investigate this, we assessed how PFC $GABA_A$ antagonism affects neuronal activation throughout the brain, indexed with the immediate early gene c-Fos. Male Long Evans rats were implanted with bilateral cannulae targeting the prelimbic PFC. A subset of animals were trained on the RM/WM task, requiring them to retrieve food from the same 4 arms of an 8-arm maze. On test days, trained and untrained rats received infusions of saline or the $GABA_A$ antagonist, bicuculline (50 ng), with some trained rats performing the task. Animals were sacrificed ~90 minutes following infusion and whole-brain tissue was processed with c-Fos immunohistochemistry. In untrained rats, PFC $GABA_A$ antagonism increased neuronal activation in cortical, ventral striatal, amygdalar and most thalamic regions, but notably, not the hippocampus. For rats trained/tested on the task. PFC $GABA_A$ antagonism increased RM and WM errors, in keeping with previous findings. These treatments also increased neuronal activation to a similar degree in trained and untrained animals in most brain regions. Strikingly, PFC disinhibition increased neuronal activation in the hippocampus only rats trained on the task. This same pattern was observed in the rhomboid thalamic nucleus. Thus, plasticity within PFC-thalamic-hippocampal circuits following hippocampal cognitive challenge may potentiate the disruptive effects of PFC disinhibition on hippocampal functioning**.** These results support to the

hypothesis that disinhibition of the PFC may cause aberrant increases in neuronal activation in efferent projection regions that, in turn, disrupt normal cognitive functioning. Further, they raise the interesting possibility that plasticity within circuits affects the extent to which PFC disinhibition alters the function of both direct and indirect projection targets. Collectively, these findings provide insight into how PFC disinhibition observed in pathological conditions such as schizophrenia impacts upon circuit function throughout the brain.

Disclosures: M. Auger: None. **J. Meccia:** None. **L.A. Galea:** None. **S.B. Floresco:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.09/SS6

Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant RGPIN-2015-05458

CFI Leaders Opportunity Fund 25026

CIHR Operating Grant MOP-133693

Title: Chemogenetic enhancement of prefrontal neuron activity facilitates the formation of precise temporal associations

Authors: *J. JAROVI[1], J. VOLLE[2], X. YU[1], K. TAKEHARA-NISHIUCHI[2]
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Abstract: The medial prefrontal cortex (mPFC) has been implicated in cognitive processes involving the linking of events across temporal delays. We recently showed artificially enhancing the activity of excitatory neurons within the mPFC enables rats to form stimulus associations over extended temporal delays that were prohibitively long for untreated rats to learn (Volle et al., 2016). This finding suggests that enhancement of the mPFC network activity improves rats' ability to detect temporal stimulus relationships: however, the enhanced learning may come with a cost of imprecision and inflexibility. Here, we examined how chemogenetic enhancement of mPFC neuron activity affects the rats' ability to discriminate a relevant temporal association from an irrelevant one and flexibly update the association in response to changes in stimulus contingency. The evolved human M3-muscarinic receptors (hM3Dq) were expressed in mPFC pyramidal neurons of adult rats via viral transduction. Neurons expressing hM3Dq were activated by systemic injection of the hM3Dq ligand, clozapine-N-oxide (CNO, 0.1 mg/kg body weight). Rats were split into two groups, where they were injected with either CNO or saline prior to daily conditioning. Each day, rats underwent two rounds of modified trace eyeblink conditioning in two conditioning chambers that differed in shape, wall pattern, floor texture, and

temperature. The first seven days of differential conditioning, rats underwent 100 trials per round where they were presented with either a light or tone conditioned stimulus (CS), where one (CS+) of which was paired with mild electric shock (US) and the other was not (CS-) in both of the conditioning environments. The next seven days of reversal learning, the previous CS+ now becomes CS-, and vice versa. During the final seven days of set-shifting, both tone and light were paired with US in the first environment, and neither were paired with US in the second environment. During the initial differential conditioning, CNO-treated rats acquired conditioned responses (CRs) to the CS+ faster than saline-treated rats, while the frequency of CRs to CS- were comparable between the groups. During reversal learning, both groups increased their responses to CS+ while decreasing responses to CS- at similar rates. There was also no difference in the speed of learning between two groups during set-shifting. Our results suggest enhancement of prefrontal neuron activity augments the formation of temporal associations without a cost to specificity or flexibility.

Disclosures: **J. Jarovi:** None. **J. Volle:** None. **X. Yu:** None. **K. Takehara-Nishiuchi:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

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Topic: H.01. Animal Cognition and Behavior

Support: NSERC Discovery Grant RGPIN-2015-05458

CFI Leaders Opportunity Fund 25026

Title: Distributed representations of temporal associations in the medial prefrontal cortex

Authors: *K. TAKEHARA-NISHIUCHI, M. D. MORRISSEY
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Abstract: The ability to link events that are separated in time is important for extracting meaning from experiences and guiding behavior in the future. One region that has been implicated in this function is the medial prefrontal cortex (mPFC), in which some neurons maintain firing responses to an event during a subsequent interval. Such persistent firings may serve as a bridge that binds two events over their intervening interval; however, they fall short of signaling exactly when the second event would take place. Motivated by recent works on temporal coding in the hippocampus, here we examined how single neurons in the mPFC encode a specific segment of temporally structured experiences. The spiking activity of individual neurons was recorded from the prelimbic region of the mPFC while rats associated a neutral conditioned stimulus (auditory or visual CS, 100 msec) with mild electric shock (US, 100 msec)

over a 500-msec interval. Consistent with previous findings, a sizable proportion of neurons changed their firing rate upon the onset of the CS and maintained the response until the onset of the US. In parallel, other cells transiently changed the firing rate during a ~100-msec segment within the CS-US interval. Some of these cells reached the peak firing rate at a comparable timing after the auditory and visual CS while others changed the peak timing depending on the CS types. At the ensemble level, a different sequential firing pattern was elicited after the auditory CS than the visual CS. The sequential firing pattern became disorganized in a block of trials during which the CS was presented by itself. It also collapsed in error trials during which the rats did not respond adaptively to the CS. Ensemble decoding analyses with support vector machine classifiers also confirmed the strong selectivity for the time segments on a trial-by-trial basis. These results suggest that prefrontal neurons use two firing modes persistent firings and sequential firings to link temporally discontiguous but correlated events.

Disclosures: K. Takehara-Nishiuchi: None. **M.D. Morrissey:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.11/SS8

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

CIHR

Title: Investigating the role of septal gabaergic and glutamatergic neurons in exploration and sleep

Authors: J. ROBINSON[1], G. DUCHARME[2], *S. EL MESTIKAWY[4], S. WILLIAMS[3]
[1]Inst. Universitaire En Santé Mentale Douglas, Montreal, QC, Canada; [2]Physiol., McGill Univ., Montreal, QC, Canada; [3]Dept Psych, McGill Univ., Verdun, QC, Canada; [4]Univ. Pierre et Marie Curie, Paris Cedex 05, France

Abstract: The medial septum and diagonal bands of Broca (MS-DBB) has an essential role in generating hippocampal rhythms as well as with learning and memory. The MS-DBB contains three main neuron populations, with each one contributing differently to the hippocampal network. The three main neuronal populations are cholinergic, GABAergic and glutamatergic. It was recently reported that optogenetic activation of GABAergic and glutamatergic neurons may modulate locomotion in terms of velocity. To compare the role of these two population in the septum, we have used optogenetics to specifically modulate each population during free exploration and sleep. Here, MS-DBB neurons were targeted with ChETA or ArchT constructs,

that were used to activate or suppress either population. Using this model, we first compare the effect of activation of GABAergic and glutamatergic neurons during locomotion, with stimulations across theta frequencies in an open field environment. Next, we examine the influence of suppressing each population during free exploration. Finally, we examine if modulating these population during REM and slow wave sleep affects sleep-wake properties. We demonstrate that activation of both GABAergic and glutamatergic neurons when stimulating at the level of the septum significantly disrupted sleep compared to controls, while stimulating at the level of the fornix had no effect. These experiments may help to determine the role GABAergic and glutamatergic MS-DBB neurons play in general exploration and sleep-wake regulation.

Disclosures: J. Robinson: None. **G. Ducharme:** None. **S. El Mestikawy:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.12/SS9

Topic: H.01. Animal Cognition and Behavior

Support: Fyssen postdoctoral fellowship

Title: Calcium imaging of medial septal glutamatergic neurons during goal-directed freely-behaving navigation

Authors: *J.-B. BOTT, E. GAUTHIER-LAFRENIERE, S. WILLIAMS
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Abstract: Using calcium photometry and optogenetic activation in head-fixed mice, it was recently proposed that medial septum glutamatergic neurons code for ongoing locomotion velocity. However, treadmill experiments limit the behavioral repertoire mainly to locomotion, and photometry do not allow for cellular resolution recordings. Thus, the role of medial septum glutamatergic cells in more complex behavioral tasks as well as the possible existence of functional sub-populations remains unexplored.
Using calcium imaging with miniaturized fluorescence microscopy, we characterized the spontaneous activity of identified glutamatergic neurons during various tasks in freely behaving mice. We show that medial septum glutamatergic neurons form an heterogeneous population of cells that are active in relation to specific behaviors. Moreover, in freely moving mice completing a goal-directed navigation task, those neurons do not code for locomotion per se but rather for trajectories.
Taken together, these results suggest that subpopulations of medial septum glutamatergic

neurons contribute differentially to hippocampal-dependent cognition and that a particular subpopulation appeared indispensable for goal directed navigation.

Disclosures: J. Bott: None. **E. Gauthier-Lafreniere:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.13/SS10

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

CIHR

Edith and Richard Strauss Postdoctoral Fellowship

Title: Role of medial septum cholinergic neurons in memory consolidation during REM sleep

Authors: *J. KANG, E. TRILLAUD-DOPPIA, S. WILLIAMS
Psychiatry, Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada

Abstract: Spatial memory has been suggested to be consolidated during rapid eye movement (REM) sleep, since disrupting Medial Septum (MS) GABAergic neurons during REM sleep has recently been shown to induce defects of spatial and contextual fear memory (Boyce et al., 2016). Interestingly, cholinergic neurons of the MS were often proposed to be a key player in memory consolidation but there is no data yet supporting this despite the evidence that MS cholinergic neurons fire during REM sleep. In this study, we have examined the effects of MS-cholinergic neuron optogenetic silencing on hippocampal activity during REM sleep and its consequences on the consolidation of contextual fear memory.
To inhibit cholinergic neurons, the inhibitory viral construct AAVdj-ArchT (n=6) or a control, AAVdj-eYFP (n=5), was injected in the MS of ChAT-Cre mice. An optic fiber was implanted in the MS and tungsten electrodes placed in the CA1 area of the hippocampus to record local field potentials. Three weeks later, mice received contextual fear conditioning (30s of cue tone followed by 50uA of electric foot shock) and were then returned to their homecage. Optogenetic silencing was performed specifically during REM sleep for a 5hr period following conditioning. On the next day, contextual and cue memory were tested by measuring the freezing duration. We found that optogenetic cholinergic silencing during REM sleep impaired contextual memory. Freezing time of the ArchT injected group was significantly reduced (79.3±12.1s, mean±sem) compared to the eYFP group (160.1±5.7s, student t-test, $p<0.01$) during context memory test. However, freezing time during the cue fear memory test was not different between the ArchT (139.6±23.7) and the control eYFP injected groups (125.2±19s). Our study suggests that

cholinergic neurons play an essential role for hippocampal-dependent contextual memory consolidation during REM sleep. We will provide experimental data on a possible mechanism involved in the role of Ach neurons in consolidation.

Disclosures: J. Kang: None. **E. Trillaud-doppia:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.14/SS11

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

CIHR

Title: Dynamically maintaining the spatial relationship of an electrical tether to a freely-behaving mouse using computer numerical control

Authors: *B. RIVARD, S. WILLIAMS
Res. Ctr., Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada

Abstract: At present, most sensors accessing the brain of a freely-behaving mouse must communicate measurements they take to remote instrumentation and analysis hardware. Though limited wireless methods exist, most instances of such communication happen through a tether cable holding lines of electrical conductor or optic fibre that course upward toward an overhead fixture. The weight and volume of this tether hinder the mouse's movement inertially and through mechanical interference with the mouse's body (when, for instance, the tether is pulled until it becomes taut and prevents the animal from moving further). Here we present a design for an active compensation to mitigate the impediment of a mouse's behavior by a tether attached to its head. The system supports the tether above the mouse's head and moves it in lock step with the animal's motion on a surface. It is composed of 1) a fiducial object video tracker that reports the cartesian spatial coordinates of colored spherical markers mounted on the animal's head, as seen from above. 2) A translation stage built with two orthogonal linear slides actuated by stepper motors, and having a range of motion corresponding to desired compensation. 3) A computer numerical controller with serial interface. A personal computer running purpose-written software converts the position coordinates from the tracker to numerical control instructions which are streamed to the hardware controller of the translation stage to which the tether is attached contiguous to the tracked markers. A full specification and characterization of this new system's performance with freely-behaving mice will be presented henceforth.

Disclosures: B. Rivard: None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.15/SS12

Topic: H.01. Animal Cognition and Behavior

Support: Alzheimer Society Doctoral Award

Brain Canada

CIHR

NSERC

Title: Deep brain stimulation improves spatial memory in an Alzheimer's disease mouse model

Authors: *E. VICO VARELA, G. ETTER, S. WILLIAMS
McGill Univ. -Douglas Mental Hlth. Uni. Inst., Montreal, QC, Canada

Abstract: Deep brain stimulation of the fornix (fDBS) has been suggested to be a potential therapeutic approach to rescue normal memory function in Alzheimer's Disease (AD). AD is a neurodegenerative disorder which has been linked to amyloid beta aggregation, marked memory deficits and early hippocampal degeneration. This study aims to identify memory-facilitation mechanisms of fDBS in the J20 transgenic AD mouse model (PDGFB-APPSwInd) by examining electrophysiological recordings of the CA1 hippocampal region. In AD and particularly in familiar forms of AD, epileptiform discharges are common and could contribute to the disease. Baseline LFP recordings of CA1 were collected in 3 to 4 months old mice during awake and sleep states, during fDBS treatment and 24 hours after fDBS treatment. Sham and experimental groups were tested in the Passive Avoidance tasks to assess spatial memory performance. We show that J20 mice display a significant impairment in memory in the Passive Avoidance task as measured by the latency to enter the dark chamber. Applying fDBS during the 24 hours after the initial learning of Passive Avoidance had a rescuing effect on memory. We show in the J20 model, that spike wave discharges in the hippocampus can be detected before amyloid-beta plaques are formed, constituting a potential early biomarker for the disease. We examine the relationship between the stimulation, behaviour and CA1 hippocampal spike wave discharges to elucidate the modulatory effect of fDBS on the memory network. We plan to optogenetically probe the septal-hippocampal circuit to assess the relationship between spike wave discharges and memory performance in AD.

Disclosures: E. Vico Varela: None. **G. Etter:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.16/SS13

Topic: H.01. Animal Cognition and Behavior

Support: Brain Canada

Title: Optogenetic stimulation of medial septum parvalbumin neurons to restore memory functions in freely moving APP Alzheimer mice

Authors: *G. ETTER, E. VICO-VARELA, S. WILLIAMS
Douglas Mental Hlth. Inst., Verdun, QC, Canada

Abstract: Alzheimer's disease (AD) has been associated with amyloid beta (Ab) aggregation, subsequent hippocampal neurodegeneration and memory defects. The exact nature and chronology of these pathological events remains largely unknown. Theta-gamma cross-frequency coupling (CFC), a physiological phenomenon that has been associated with memory encoding and retrieval, has been previously shown to be decreased in complete hippocampal preparations from 3 weeks old transgenic AD mice model. In the present study, we have monitored CA1 local field potentials in the freely behaving J20 AD mice model (PDGF-APPSw, Ind) trained to seek a reward on a modified appetitive version of the Barnes maze as well as during REM sleep. At 6 months, J20 mice display more spatial errors as well as non-targeted exploration during the probe trial compared to non-transgenic (NTg) counterparts. We found that theta-gamma CFC is significantly reduced during REM sleep, while it is abolished when mice actively explore the Barnes maze. We propose that these pathological oscillations underlie the cognitive defects observed in Alzheimer's condition. Consequently, reinstatement of normal oscillations could lead to improved memory functions. To test this hypothesis, we propose to combine *in vivo* electrophysiological recordings in freely behaving mice with optogenetics, so as to manipulate experimentally and enhance neuronal networks that underlie hippocampal oscillations in J20 Tg+ mice. Parvalbumin (PV) interneurons of the medial septum send long-range projections to the hippocampus and have been recently shown to robustly drive hippocampal oscillations. Using J20 AD x PV-Cre crossed mice and optogenetics, we stimulated PV interneurons of the medial septum with light and were able to pace hippocampal oscillations at different desired frequencies. Using gamma range optogenetic stimulations, we were able to increase both gamma power and coupling to theta oscillations, thus reinstating normal oscillation patterns. This study suggests that circuits underlying cross-frequency coupling are affected very early in AD mice models and might underlie the spatial memory defects and suggests that the CFC may be an early biomarker of AD. We propose that selective stimulations of medial septum

PV interneurons and re-establishments of normal rhythmic activity could be a new therapeutic strategy to restore memory defects in AD conditions.

Disclosures: G. Etter: None. **E. Vico-Varela:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.17/SS14

Topic: H.01. Animal Cognition and Behavior

Support: NSERC

CIHR

Title: Simultaneous multi-region calcium imaging in freely behaving mice

Authors: *L. PENAZZI[1], J.-B. BOTT[1], Y. SOUDAGAR[2], E. LAFRENIERE[1], F. MANSEAU[1], B. RIVARD[1], S. WILLIAMS[1]
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Abstract: Understanding how neural networks dynamically coordinate during learning and memory processes remains an open question. The recent innovative advances in optical technologies have enabled the longitudinal recording of the activity of large number of neurons in freely behaving mice. Such techniques allow scientists to establish a causal connection between brain function, the dynamic of its network and memory performances. Head-mounted fluorescent miniature microscope (miniscope) is one leading technology, that has raised a great deal of interest in the scientific community. This technique is based on the implantation of a GRIN lens above the region of interest in which neurons express a calcium indicator such as GCaMP6 fast. However, although this device is capable of imaging hundreds of neurons in a given area, its design makes imaging more than one brain region almost impossible. We present here an innovative endoscopic device developed by Neurescence Inc., which enables the simultaneous imaging of multiple brain areas in freely behaving mice. Its optimized design is based on a high flexibility in connecting multiple independent fibers to individual implanted lens. This new technology offers an easy combination of wide-field fluorescent imaging with electrophysiological recordings from both superficial and deep brain areas by the assembly of recording electrodes with lenses with various diameters and lengths. In this project, we employed the Neurescence imaging device to simultaneously record bilateral hippocampal neuronal activity from either principal neurons or interneurons. To assess neuronal activity, the calcium indicator GCaMP6 fast was expressed using viral vectors injected into the CA1 area before

implantation of the lenses. Calcium transients were recorded from adult VGAT-cre mice performing open-field, T-maze and a spatial allocentric navigation task.

Disclosures: L. Penazzi: None. **J. Bott:** None. **Y. Soudagar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurescence Inc. **E. Lafreniere:** None. **F. Manseau:** None. **B. Rivard:** None. **S. Williams:** None.

Poster

166. Learning and Memory: Hippocampal-Prefrontal-Basal Forebrain Interactions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 166.18/SS15

Topic: H.01. Animal Cognition and Behavior

Support: NIMH 1R01MH100631

Title: Dynamics of cholinergic modulation in hippocampal region CA1 during context exploration and goal oriented learning

Authors: *R. NYILAS, J. B. PRIESTLEY, IV, W. LI, E. M. BALOUGH, J. C. BOWLER, A. LOSONCZY
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Abstract: Elevated cholinergic activity has been associated with various brain states and processes, such as arousal, attention, and learning. Acetylcholine (ACh) is thought to enhance neuronal responses to sensory stimuli and facilitate cortical plasticity during encoding of new information. One of the main targets of cholinergic modulation is the hippocampal network (HPC), which is critical for spatial and episodic memory formation in the mammalian brain. Accordingly, perturbations of ACh input to the HPC cause severe deficits in spatial navigation and hippocampal learning. However, the activity of cholinergic cell output and its specific influences *in vivo* on network operations and behavior remain unclear. To elucidate these dynamics, we registered the activity of cholinergic fibers in the HPC (1) during exploration of different contexts, (2) in response to various sensory stimuli, and (3) concomitant with behavioral correlates of spatial learning. We selectively labeled cholinergic neurons of the anterior basal forebrain with the functional calcium indicator GCaMP6f via viral gene transfer and transgenic ChAT-Cre mice. Using *in vivo* 2-photon imaging in head-restrained animals, we achieved chronic recordings of the axonal projections of these neurons in dorsal CA1 of the HPC with single-fiber resolution, while animals ran on a linear treadmill. In our preliminary experiments, cholinergic axons in CA1 stratum oriens exhibited robust running-related activation. During immobility, ACh tone was high in a novel environment (characterized by distinct auditory, olfactory and tactile contextual cues), and gradually decreased in time, as the

context became familiar. Individual fibers were transiently activated by sensory stimuli (light and tone), and responded strongly to stimuli with special valence (water and airpuff). In a goal-oriented spatial learning task (Danielson et al, 2016), cholinergic activity decreased in the first few laps as the animal learnt the position of the reward and suppressed licking outside the reward zone. Additionally, a strong decline of cholinergic activity accompanied the anticipatory/post-reward licking around the rewarded area. Strikingly, when the location of the reward zone was changed, we detected a temporary elevation in ACh activity. In further analysis, we aim to decipher the fine grained pattern of cholinergic activity in correlation with the various stages of hippocampal information processing and behavior.

Disclosures: **R. Nyilas:** None. **J.B. Priestley:** None. **W. Li:** None. **E.M. Balough:** None. **J.C. Bowler:** None. **A. Losonczy:** None.

Poster

167. Human Long-Term Memory: Declarative

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 167.01/SS16

Topic: H.02. Human Cognition and Behavior

Support: NIMH MH060941

Title: Neural activity associated with repetitive simulation of episodic counterfactual thoughts

Authors: *F. DE BRIGARD[1], N. PARIKH[2], G. W. STEWART[3], K. K. SZPUNAR[4], D. L. SCHACTER[5]
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Abstract: When people revisit past autobiographical events they often imagine alternative ways in which such events could have occurred. Often these episodic counterfactual thoughts (eCFT) are momentary and fleeting, but sometimes they are simulated frequently and repeatedly. Indeed, repetitive counterfactual simulation has been strongly associated with generalized anxiety with and without depression. However, little is known about the neural differences between frequently repeated versus non-repeated eCFT. The current study explores this issue. 19 individuals participated in this three-session study. In session 1, participants reported 110 specific autobiographical memories, providing valence ratings for each one of them. In session 2, which took place a week later, 90 of their reported memories were assigned to one of three counterfactual conditions. In the upward counterfactual condition, participants imagined alternative better ways a remembered negative event could have occurred. In the downward counterfactual condition participants imagined an alternative worse way in which a remembered positive event could have occurred. And in the neutral counterfactual condition participants

imagined alternative ways the event could have occurred without changing its valence. Session 3 took place a day later and had two parts. First, participants were asked to re-simulate 15 upward, 15 downward and 15 neutral counterfactuals, randomly selected, and 3 times each. Second, participants were presented with all 90 simulated counterfactuals while undergoing fMRI, and were asked to recognize whether or not they had re-simulated each counterfactual earlier that day. Additionally, ratings of novelty, detail and plausibility were collected. A mean-centered partial least squares (PLS) analysis on the fMRI data was conducted. This analysis revealed that eCFT that were not frequently repeated preferentially engaged brain regions including middle (BA 21) and superior temporal (BA 38/39), middle (BA 11) and superior frontal (BA 9), and hippocampus. By contrast, frequently repeated eCFT preferentially engaged regions including medial frontal (BA 10), anterior cingulate, insula and inferior parietal (BA 40). Direct contrasts for each type of eCFT were also conducted, revealing precise contributions of each valence to the overall pattern of activation. These results suggest differential contributions of regions traditionally associated with eCFT, such as BA 10, anterior cingulate cortex, and hippocampus, as a function of frequency of repetition. Consequences for future research on eCFT and rumination in the context of anxiety are explored.

Disclosures: **F. De Brigard:** None. **N. Parikh:** None. **G.W. Stewart:** None. **K.K. Szpunar:** None. **D.L. Schacter:** None.

Poster

167. Human Long-Term Memory: Declarative

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Program#/Poster#: 167.02/SS17

Topic: H.02. Human Cognition and Behavior

Support: DFG research grant: SCHW 1357/12-1

Title: Imaging memory transformation: Neural signature of detailed and gist-like memories of recent and remote events

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Abstract: Over time, memories undergo a neural reorganization. Yet the exact nature of this reorganization is still debated. According to the Standard Consolidation Theory, memories are gradually consolidated from the hippocampus to the neocortex until they are ultimately independent of the hippocampus. The Memory Transformation Hypothesis, however, postulates that memories undergo a transformation from detailed, episodic to gist-like, semantic representations and that while these semantic memories can be retrieved solely from the neocortex, the detailed episodic memories would always remain hippocampus-dependent. The

present experiment contrasted these views and tested the transformation of episodic memories as well as the neural changes associated with memory over time. Forty-eight participants encoded pictures and performed a recognition test in the MRI scanner either 1 day or 28 days after encoding. Critically, the recognition test contained the original pictures, entirely novel pictures, as well as similar pictures carrying the gist of the original ones, thus allowing us to assess the specificity of memory. Overall, memory performance in the 28 days group was reduced compared to the 1 day group. Importantly however, twenty-eight day old memories were characterized by a lack of memory specificity, reflected by a significantly elevated false alarm rate for similar pictures, in comparison to the false alarm rate for entirely novel pictures. Imaging data showed significantly less activity in the anterior hippocampus, mid-portion hippocampus and entorhinal cortex after 28 days (vs. 1 day), whereas activity in the posterior hippocampus and most neocortical areas did not differ significantly between the two groups.

Disclosures: L.C. Dandolo: None. **L. Schwabe:** None.

Poster

167. Human Long-Term Memory: Declarative

Location: Halls A-C

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Program#/Poster#: 167.03/SS18

Topic: H.02. Human Cognition and Behavior

Support: The Knut and Alice Wallenberg Foundation's Network Initiative on Culture, Brain, and Learning

NIH F32AG056080

Title: Hippocampal contribution to cortical reinstatement during episodic retrieval

Authors: *J. JIANG[1], K. F. LAROCQUE[2], S. GUERIN[3], C. FERNANDEZ[4], A. D. WAGNER[2]
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Abstract: A hallmark of human episodic memory is the ability to retrieve event-specific information. For example, out of many restaurants in memory, you can remember the exact one you went to last night. Successful episodic retrieval is accompanied by cortical reinstatement, or retrieval-stage reactivation of neural activity patterns that were present at encoding. Category-specific and item-specific cortical reinstatement have been observed in multiple areas, including inferior parietal cortex (IPC) and ventral occipitotemporal cortex (VOTC), and have been linked to hippocampal retrieval activity. However, how item-level cortical reinstatement at retrieval is linked to hippocampal mechanisms at encoding remains largely unknown. We acquired fMRI data while participants (N=16) performed a one-shot associative learning task followed by associative retrieval (cued recall). During encoding, participants formed associations between

words and images (natural or manmade objects); during retrieval, subjects were presented the words and were instructed to recall the associated image. From anatomically defined IPC and VOTC ROIs, we extracted trial-wise fMRI activity patterns from the encoding and retrieval phases, and calculated the encoding-retrieval similarity (ERS) of activity patterns. ERS was calculated for three conditions based on the relationship between the image presented in the encoding trial and the image associated with the cue in the retrieval trial: namely the same image (within-item pair), different images in the same category (within-category pair) and different images in different category (across-category pair). Initial results revealed greatest ERS for within-item pairs relative to within-category and across-category pairs in both IPC and VOTC. Within-item ERS was also the highest when participants correctly retrieved the category of the associated image. Moreover, hippocampal univariate activity during retrieval positively correlated with within-item ERS in IPC and VOTC. These results replicate and extend previous findings documenting item-level cortical reinstatement in IPC and sensory cortex. Future analyses will examine the relationship between cortical reinstatement and hippocampal mechanisms at encoding (e.g., pattern separation).

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Poster

167. Human Long-Term Memory: Declarative

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Topic: H.02. Human Cognition and Behavior

Support: SFB 776A7

HBP SP3 Wp 3.3.1

Medical Research Council and Wellcome Trust, UK

Title: Hippocampal subfield contributions to the recollection of multi-element events: Functional evidence at 7 tesla

Authors: *X. GRANDE[1,2], J. A. BISBY[3,4], D. BERRON[1,2], A. J. HORNER[5], E. DUZEL[1,2,3], N. BURGESS[3,4]
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Abstract: In humans, the role of the hippocampus in recollection of multi-element events based on partial cues has been shown recently (Horner, Bisby, Bush, Lin, & Burgess et al., 2015). Theoretical models and animal studies, however, suggest that there are differential functional contributions from hippocampal subfields. At recollection, hippocampal subfield CA3 seems to be specifically involved in the completion of partial cues whereas CA1 is suggested to be important for the cortical reinstatement of the completed pattern. Here, we used the same multi-element events paradigm and acquired magnetic resonance imaging functional data (EPI) with submillimetre (0.8 mm isotropic) resolution at 7 Tesla. In addition we obtained high-resolution T2-weighted structural images (0.4 x 0.4 x 1 mm). The ultra-high resolution images allowed us to manually delineate hippocampal subfields and analyse their specific role in the recollection of multi-element events in humans. In line with previous research, we found increased activity in CA3 the better an event is remembered. Activity in subfield CA1 and Subiculum correlates significantly with cortical reinstatement. As we obtained data from the encoding phase as well, we also investigate the specific involvement of subfields in hippocampal binding and its relation to subsequent recollection. The study sheds light on the role of the human hippocampal circuitry in successful binding and recollection of episodic events.

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Poster

167. Human Long-Term Memory: Declarative

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Program#/Poster#: 167.05/SS20

Topic: H.02. Human Cognition and Behavior

Support: Natural Sciences and Engineering Council of Canada

Title: Identifying multivariate representations associated with temporal duration information in the context of individual event sequence memories

Authors: *S. THAVABALASINGAM[1], E. B. O'NEIL[1], J. TAY[1], A. NESTOR[1], A. C. LEE[1,2]
[1]Psychology (Scarborough), Univ. of Toronto, Toronto, ON, Canada; [2]Rotman Res. Institute, Baycrest Ctr., Toronto, ON, Canada

Abstract: Our memories are rich with temporal information, enabling us to remember when a past event took place. Although a number of studies have examined how medial temporal lobe (MTL) structures contribute to temporal context, order and distance information in the service of episodic memory (e.g. Ezzyat and Davachi, 2014; Hsieh et al., 2014; Jenkins and Ranganath, 2010; Kumaran and Maguire, 2007), the neural correlates associated with temporal duration memory, for instance memory for the amount of time that has elapsed between successive

events, has been relatively under-explored. To address this issue, the current study sought to investigate whether multivariate patterns of functional magnetic resonance imaging (fMRI) data can capture information pertaining to the temporal duration structure of individual memories. Neurologically healthy participants first learned four separate sequences of scene images that differed along two dimensions of content (scene identity) and temporal structure (stimulus interval duration) in a 2 x 2 factorial design. High resolution fMRI data were then acquired while the participants identified the different event sequences in a recognition memory task. Multivariate analyses including multivoxel pattern classification and information-based connectivity were then used across a number of regions of interest, including MTL structures, to explore the activity associated with each of the learned sequences. Our findings provide further insight into the neural correlates of temporal duration memory and how temporal information can shape our mnemonic representations.

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Poster

167. Human Long-Term Memory: Declarative

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Program#/Poster#: 167.06/SS21

Topic: H.02. Human Cognition and Behavior

Support: RGPIN-04241

Title: The neural basis of thematically and spatially guided recall of recent and remote autobiographical memories

Authors: *L. GURGURYAN, S. SHELDON
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Abstract: Autobiographical memories can be remembered in different ways, yet how these differences are reflected in the brain is unclear. One brain region that is critical for orchestrating the neural activity associated with remembering past experiences is the hippocampus. A new view of hippocampal function is that there is a division of labour along the longitudinal axis, proposing that anterior and posterior regions may support different ways of remembering. Here, we characterized the patterns of hippocampal and cortical activity that distinguish between remembering thematic and spatial elements of recent and remote autobiographical experiences. In a MRI scanner, 24 participants completed experimental trials that began with remembering a pre-selected autobiographical memory (6 recent and 6 remote events). Next, participants focused on either the thematic (conceptual condition) or spatial (contextual condition) elements of that memory and then used the recovered details to access and elaborate on a new memory. Across

all forms of memory retrieval, the contextual condition was associated with preferential activity in the occipital, posterior parietal, and medial temporal lobes whereas the conceptual condition was associated with preferential activity in anterior and midline brain structures. Within the hippocampus, posterior regions preferentially supported the contextual condition and anterior regions preferentially supported the conceptual condition. When considering memory age, there were no activity differences within the hippocampus between recent and remote memories; however, at the whole-brain level, there was preferential activity in the posterior parietal cortex for retrieving spatial details of recent memories (the contextual condition). Thus, memory age affects the neural differences observed between spatially and thematically guided remembering. In support, a hippocampal ROI analysis for recent memory trials revealed increased posterior hippocampal activity for the contextual condition, however, for remote memory trials, there was increased anterior hippocampal activity for the conceptual condition. Together, these data indicate that how a memory is recalled and reconstructed can fundamentally alter the underlying patterns of neural activity. Moreover, our data suggest that certain anterior/posterior hippocampal processes are predisposed toward certain forms of remembering that is dependent on the age of the retrieved memory.

Disclosures: L. Gurguryan: None. **S. Sheldon:** None.

Poster

167. Human Long-Term Memory: Declarative

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McKnight Endowment Fund for Neuroscience

NARSAD

Title: Long range cortical, but not local, substantia nigra single neuron spike field coherence predicts successful declarative memory formation in humans

Authors: *J. KAMINSKI[1,4], A. MAMELAK[1], K. BIRCH[1], M. TAGLIATI[2], U. RUTISHAUSER[1,4,2,3]
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Abstract: Learning from novel experience is a fundamental task of the human brain. Dopamine (DA) is a crucial neuromodulator for memory formation because it modulates synaptic plasticity. In addition, high coordination of spike timing is also essential for synaptic plasticity. DA neurons in the substantia nigra (SN) project to the hippocampus and it is thus thought that the SN has a role in declarative memory formation. We recorded single neurons in the SN of patients undergoing implantation of a deep brain stimulation device in the subthalamic nucleus (STN), to assess the role of spike-field coherence (SFC) of substantia nigra (SN) neurons on memory formation. We presented awake patients (n=26 sessions in 22 patients) with a sequence of images and asked them to classify each as novel or familiar. Simultaneously, we recorded single unit neuronal activity (n=64 neurons) in the SN and local field potentials (LFPs) from the STN. Additionally, we recorded cortical activity using ECOG recordings performed with an electrode strip placed on sensory, motor and premotor cortex. We found that a subset of 14/64 of SN neurons indicated whether a stimulus was novel or familiar, supporting the view that the SN carries signals related to declarative memory. We further found that SN neurons showed field coherence in theta (3-8 Hz) band range with both STN and the premotor cortex. An analysis of SFC encoding period of novel images showed that successful memory formation was associated with significantly stronger long-range theta spike field coherence with premotor cortex. In contrast, we did not observe a difference between remembered and forgotten images in SFC of SN neurons relative to the STN LFP. These results suggest that successful memory formation depends on tight synchronization of neuronal activity of distributed networks in the brain.

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Poster

167. Human Long-Term Memory: Declarative

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Topic: H.02. Human Cognition and Behavior

Support: NRF Grant 2015R1A2A2A03004026

Title: Functional network of medial prefrontal cortex compensates episodic memory function following medial temporal lobe resection

Authors: *W. JEONG[1,2], H. LEE[4], J. KIM[3], C. CHUNG[1,2,3]
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Abstract: Purpose: Considering the central position of the hippocampus as a densely interconnected hub in brain networks and its role in episodic memory, medial temporal lobe resection (MTLR) including hippocampus should modify recruitment and strength of connectivity of functional memory network. However, successful reorganization of functional memory network in patients with MTLR has not been demonstrated which could provide a clue for new therapeutic targets for people with memory impairment. In the present study, we aim to understand effective episodic memory reorganization following MTLR in a new perspective of functional connectivity of memory network.
Methods: We studied 37 patients who underwent unilateral MTLR for the treatment of medically intractable epilepsy (17 left, 20 right; median age 34 years) and 24 healthy controls (median age 32 years). All patients showed at least worthwhile seizure reduction after surgery, and the majority of the patients (84%) achieved seizure free outcome (mean follow-up = 6.45±2.75 years). All subjects performed functional MRI memory encoding paradigm of words and abstract figures followed by out-of-scanner recognition test. Functional imaging data were analyzed using AFNI software.
Results: Both patients groups exhibited normal range of memory capacity after surgery. In the hippocampal ROI analysis, we found that greater contralateral hippocampus activation was related to higher postoperative memory scores in both patient groups. Whole-brain task-based functional connectivity analysis revealed that the right medial prefrontal cortex (mPFC) showed stronger interactions with widespread brain areas including contralateral hippocampus during word encoding in left MTLR group and during figure encoding in right MTLR group. We also found that the strength of right mPFC functional connectivity predicts verbal memory scores in left MTLR patients and visual memory scores in right MTLR patients.
Conclusions: Thanks to the relatively long follow-up period, we could investigate stable memory encoding network after functional reorganization process in postoperative patients with unilateral MTLR. We found that engagement of the contralateral hippocampus after unilateral MTLR is persisted long-after surgery and it represents effective compensatory reorganization. We also suggest that hyper-connectivity of mPFC may play a compensatory role in episodic memory function for the loss of functional connections of MTLs. Therefore, we suggest that the medial PFC could be a possible future target area for the brain stimulation toward enhancing memory function in people with MTL dysfunction-related memory disturbances.

Disclosures: **W. Jeong:** None. **H. Lee:** None. **J. Kim:** None. **C. Chung:** None.

Poster

167. Human Long-Term Memory: Declarative

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Topic: H.02. Human Cognition and Behavior

Support: Intel Labs

NIH grant R01 MH112357-01

Title: Perception and recall of narrative event schemas

Authors: *C. BALDASSANO, R. MASIS-OBANDO, U. HASSON, K. A. NORMAN
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Abstract: Understanding movies and stories requires maintaining a high-level "situation model" (Zwaan and Radvansky 1998) that abstracts away from particular perceptual details to describe the location, characters, actions, and causal relationships of the currently unfolding event. Situation models draw on prior knowledge about event schemas, which describe typical event sequences encountered throughout a lifetime (Piaget 1926; Bartlett 1932; Schank and Abelson 1977; Zacks et al. 2007).

Based on studies in both rodents (Tse et al. 2011) and humans (van Kesteren et al. 2010; Brod et al. 2015), the use of schemas at encoding and retrieval is thought to be modulated primarily by the medial prefrontal cortex (mPFC). The majority of these paradigms, however, have only contrasted schema-consistent stimuli with schema-inconsistent stimuli. It is therefore unclear whether mPFC simply detects whether a schema is present, or if it represents information about the specific schema being experienced. Additionally, neuroimaging studies largely use simplified associative schemas, rather than temporal sequences of real-world narrative events.

We presented 31 subjects with sixteen stories, eight that shared one narrative schema (eating at a restaurant) and eight sharing a second (catching a flight at an airport), but all differing extensively in terms of characters, timing, plot, and modality (audiovisual movies or audio narration). Whole-brain fMRI data was recorded while subjects watched and listened to the stories, and then while subjects freely recalled all sixteen stories. We computed the average activity pattern evoked by each story during each of four schematic subevents (e.g. entering the airport, going through security, walking to the gate, and boarding the plane), and measured the consistency of subevent patterns across different narratives with a shared schema.

We find the strongest across-narrative schema representations in mPFC ($p<0.001$) and the hippocampus ($p=0.008$). In both of these regions, the recall performance of each subject was predicted by the similarity of the subject's story-specific event representations to the group average (mPFC: Spearman's rho = 0.33, $p<0.001$; hippocampus, Spearman's rho = 0.17, $p=0.040$). Critically, subjects whose event representations in mPFC were more schematic (more similar across stories within the same schema) exhibited more extensive recall (Spearman's rho = 0.21, $p=0.034$). These results show that mPFC is engaged to represent realistic autobiographical schemas that are learned over a lifetime, and suggests that schematic activation in mPFC is a critical component of successful memory encoding and retrieval.

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Poster

167. Human Long-Term Memory: Declarative

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Topic: H.02. Human Cognition and Behavior

Support: NIH-NINDS 1RO1NS089729

Title: Understanding the relationship between repetition priming and episodic memory

Authors: *G. KIM, B. A. KUHL
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Abstract: When a stimulus is repeatedly encountered, this creates an opportunity for its memory trace to be modified. A fundamental goal of memory research is to understand how memory representations change as a function of repetition. In particular, several previous studies have investigated the relationship between repetition-related increases in processing speed (repetition priming) and subsequent recognition memory (an index of episodic memory). However, no clear relationship between repetition priming and episodic memory has been established. While there are likely many factors that complicate the relationship between priming and episodic memory, here we considered the possibility that priming may differentially relate to episodic memory according to the form of episodic memory that is tested. In particular, we hypothesized that repetition will influence the distinctiveness of a stimulus relative to other, similar stimuli. If so, then repetition priming should differentially predict episodic memory in tasks where discrimination between similar stimuli is irrelevant (e.g., simple recognition memory decisions) vs. tasks where discriminating between similar stimuli is relevant (e.g., associative interference). We tested this hypothesis across a series of behavioral studies that shared the same general structure. To measure repetition priming, participants made speeded indoor/outdoor judgements for various scene images in an initial phase. Priming was defined as faster reaction times for a repetition of a stimulus relative to its initial presentation. Importantly, the set of scene images we used contained various categories of images (e.g., beaches), with several similar exemplars per category. In a second phase, we tested episodic memory either via an item recognition test (old vs. new) or an associative learning task that (critically) placed demands on discriminating between exemplars from a common category. For each task, we assessed the relationship between repetition priming and episodic memory (either recognition or associative) on an item-by-item basis. Consistent with our hypothesis, we found that repetition priming was differentially related to performance on the recognition memory and associative interference tasks: greater priming tended to predict relatively worse performance on the recognition memory task and relatively better performance on the associative interference task. These findings inform understanding of how memory representations are adaptively updated by repeated experiences.

We consider the potential relevance of these findings to theoretical models of neural repetition suppression.

Disclosures: G. Kim: None. **B.A. Kuhl:** None.

Poster

167. Human Long-Term Memory: Declarative

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 167.11/SS26

Topic: H.02. Human Cognition and Behavior

Title: Dynamic functional connectivity during incidental memory encoding: A functional magnetic resonance imaging (fMRI) study

Authors: *R. KEERATIVITTAYAYUT, R. AOKI, K. NAKAHARA
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Abstract: Humans have an amazing ability to remember daily episodes without efforts or intentions. Previous studies showed that neural activity in the human medial temporal lobes (MTL) can predict subsequent memory performance, i.e., subsequent memory effect (SME). On the other hand, subsequent forgetting effect (SFE) during poor encoding was observed predominantly in the default mode network (DMN). However, dynamic functional connectivity (FC) changes between successful and poor encoding phases remain unclear. In our fMRI study, we used semantic judgement task as a sham task to investigate incidental memory encoding of visual stimuli and applied graph theoretical measures to characterize dynamic change in global FC. Twenty-four participants participated incidental memory encoding scans followed by a surprise memory test. Each encoding trial was classified into successful encoding trial or unsuccessful encoding trial based on answers from the surprise memory test. Signal time courses during encoding were extracted from regions of interest (ROI) across the entire brain and then divided into time windows (window size = 50TR or 36s). Each window was classified into success state or unsuccessful state based on the amount of successful encoding trials within each time window. Within each state, graph measures were calculated to obtain FC patterns. We observed significant increase of global modularity and clustering coefficient during the successful state. Importantly, SME related network increased within network connectivity during successful encoding. In contrast, during unsuccessful encoding the SME related area rather increased across network connectivity to SFE related networks. Our predominant finding is that the brain dynamically transverses between successful and unsuccessful states by reorganizing its global FC pattern between segregated and integrated states, respectively. These results suggest that the segregation across brain regions supports the successfully incidental encoding. The higher connectivity within SME network supports more efficient encoding, but connectivity from

SME network to other areas cause less efficiency. In conclusion, our findings emphasize a role of FC across brain regions, both inside the MTL and cortical area in memory encoding.

Disclosures: R. Keerativittayayut: None. **R. Aoki:** None. **K. Nakahara:** None.

Poster

167. Human Long-Term Memory: Declarative

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 167.12/SS27

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21NS095094

Title: Encoding related modulation of regional activity differs depending on how memory is tested

Authors: *D. R. KING[1], B. C. LEGA[2], M. D. RUGG[3]
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Abstract: Numerous fMRI studies have examined differences in neural activity elicited by study items according to whether the items were later remembered or forgotten (subsequent memory effects or SMEs). The great majority of these studies employed some version of a recognition memory test to assess subsequent memory, whereas far fewer have employed a test of free recall. Here, we compared SMEs elicited by the same set of study items but defined according to whether memory for the items was later tested with a free recall or a recognition memory test. Twenty participants underwent fMRI scanning while they were administered 18 repeated study-test cycles. In the study phase of each cycle, 15 concrete nouns were visually presented and participants were instructed to imagine the referent of the cue word. Following a 15 second distractor task, participants verbally recalled as many of the words from the immediately preceding list as possible. After exiting the scanner, participants were administered a surprise recognition test comprising all of the studied words intermixed with 135 new words. For each test item, participants simultaneously made an old/new recognition memory judgment along with a 2-way (high, low) confidence judgment. In two separate analyses of the fMRI data acquired during the study phases of each cycle, study trials were categorized and encoding-related activity contrasted according to whether studied items were subsequently recalled (recall success versus recall failure) or recognized (high confidence recognition hits versus misses). The loci and characteristics of the SMEs associated with successful recall and recognition performance varied markedly. ‘Positive’ SMEs (greater BOLD signal for later remembered items) were identified in a variety of cortical regions, only one of which - left inferior frontal gyrus - overlapped between

the two memory tests. We were unable to identify effects in the medial temporal lobe for either test. More strikingly, 'negative' SMEs (lower activity for later remembered items) were evident for successfully recognized items only. These findings point to a key role for the left inferior frontal gyrus in supporting verbal memory encoding. In addition, while there are numerous possible reasons for these task-based dissociations in SMEs - e.g., differences in retrieval context (inside or outside the scanner) or study-test delay - the findings illustrate the sensitivity of SMEs to when and how memory is later tested.

Disclosures: D.R. King: None. **B.C. Lega:** None. **M.D. Rugg:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.01/SS28

Topic: H.02. Human Cognition and Behavior

Support: R01MH111790

R01MH106512

Title: Enhanced stimulus-evoked hippocampal-cortical activity during memory formation following network-targeted noninvasive brain stimulation

Authors: *S.-S. KIM[1], M. S. HERMILLER[1], R. PALUMBO[1], S. A. VAN HAERENTS[2], J. L. VOSS[1]
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Abstract: Previous findings have shown that multi-day repetitive transcranial magnetic stimulation (rTMS) targeting the hippocampal-cortical network enhances fMRI connectivity of the network, including especially connectivity of hippocampus with posterior-medial occipitoparietal regions. Here, we investigated stimulation-caused changes in stimulus-evoked activity of this network during memory formation. Young healthy adults (N=16; ages 18-34 years) received multi-day 20-Hz rTMS to a left parietal cortex region defined by high fMRI connectivity with the body of left hippocampus. They performed object-scene and object-location association memory tasks during fMRI scanning before and 24 hours after stimulation. Relative to a sham-stimulation condition, stimulation caused significantly enhanced evoked activity to later-remembered stimuli in a region of the left hippocampus slightly posterior to the specific location that was targeted, as well as in a corresponding region of right hippocampus. Heightened evoked activity was also identified in posterior-medial occipitoparietal regions that were previously shown to increase in fMRI connectivity with the hippocampus due to stimulation. The effects were more robust for object-scene than object-location memory

formation. These results suggest that targeted rTMS can selectively enhance evoked activity of the hippocampal-cortical network, suggesting that stimulation increases excitability of the network during memory formation.

Disclosures: S. Kim: None. **M.S. Hermiller:** None. **R. Palumbo:** None. **S.A. Van Haerents:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.02/SS29

Topic: H.02. Human Cognition and Behavior

Support: NIH R01-MH111790

NIH NS047987

Title: Frequency-specific noninvasive modulation of hippocampal-cortical networks and memory

Authors: *M. S. HERMILLER[1], D. J. GREEN[2], S. VANHAERENTS[3], T. RAIJ[6,4], D. J. BRIDGE[1], J. L. VOSS[1,3,5]
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Abstract: The hippocampal-cortical network has been associated with a variety of memory abilities, including familiarity and recollection. Neural activity in this network has been shown to synchronize at theta frequency, providing a possible correlate of communication among network regions important for memory. Here we tested whether stimulating the hippocampal-cortical network noninvasively at theta frequency has a greater effect on network fMRI connectivity and memory compared to non-theta stimulation. We have previously shown increases in fMRI connectivity and associative memory due to multi-day 20-Hz repetitive transcranial magnetic stimulation (rTMS). We therefore compared 20-Hz rTMS to theta-burst stimulation (TBS), which involves 50-Hz bursts of stimulation at 5 Hz. In this multi-day, within-subject design, we compared the effects of intermittent TBS, continuous TBS, and 20-Hz rTMS relative to sham on memory performance and fMRI connectivity. On each day, participants (N=24) studied 96 unique words presented in one of eight colors, after which MRI-navigated brain stimulation was delivered to the lateral parietal cortex. Immediately following stimulation, resting-state fMRI was performed and then participants completed a memory test including item recognition and source memory (word color). Recognition accuracy measured as discrimination sensitivity (d') was greater following continuous TBS relative to sham ($P<0.02$) and relative to 20-Hz rTMS

(P<0.05). Each stimulation condition significantly modulated fMRI connectivity within the hippocampal-cortical network, as measured via within-network fMRI connectedness values (voxel-wise P<0.001). Changes in fMRI connectivity due to intermittent and continuous TBS were more broadly distributed throughout the network and more robustly involved the hippocampus compared to 20-Hz rTMS changes, which were constrained to medial regions. For the continuous TBS condition, increased fMRI connectivity between the precuneus and anterior cingulate cortex predicted corresponding increases in recognition accuracy, relative to sham (P<0.01). These findings indicate that the hippocampal-cortical network and the memory abilities that it supports are more robustly engaged by noninvasive stimulation delivered at endogenously generated frequency related to network interconnectivity. These findings help validate specific engagement of the hippocampal-cortical network by targeted noninvasive stimulation and have implications for the optimization of noninvasive stimulation for targeting hippocampal-cortical memory networks.

Disclosures: M.S. Hermiller: None. **D.J. Green:** None. **S. VanHaerents:** None. **T. Raij:** None. **D.J. Bridge:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

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Program#/Poster#: 168.03/SS30

Topic: H.02. Human Cognition and Behavior

Support: R01-MH111790

R01-AG049002

T32-AG20506

Title: Is memory precision supported by a hippocampal-cortical network? Evidence from brain lesions and noninvasive stimulation

Authors: *A. NILAKANTAN[1], D. J. BRIDGE[2], S. A. VANHAERENTS[3], J. L. VOSS[2]
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Abstract: Episodic memory has been associated with the hippocampus and a network of cortical brain regions, including medial prefrontal and lateral parietal cortex. Most studies explore *memory success* but do not consider the varying amounts of qualitative detail (*memory precision*) successfully recalled. A handful of conflicting studies have suggested that memory precision is supported by either the parietal cortex or hippocampus alone. Here, we test a consensus position that emphasizes the possible reliance of memory precision on the hippocampal-cortical network.

Eighteen healthy young adults and 9 adults with unilateral temporal lobe resection (including hippocampus) participated in an associative object-location memory test designed to segregate memory success from memory precision. Participants studied unique objects at random distinct locations, and after a delay were instructed to recall each object's studied location. Success was defined as the proportion of trials successfully recalled within the same quadrant in which the object was studied, while precision was defined as the mean distance error of those successful trials. Relative to young healthy adults, success was relatively matched for participants with unilateral temporal resection ($p>0.1$), while precision was significantly impaired ($p<0.001$). Furthermore, the total amount of temporal tissue resected was related to precision ($r=0.6$, $p=0.08$) but was unrelated to success ($r=0.1$, $p>0.7$). These data highlight the necessary role of the hippocampus and surrounding medial temporal lobe in precision. In a second study, we sought to test the causal role of the hippocampus and its interaction with its cortical network in precision. Our preliminary data in N=16 young adults indicated that noninvasive brain stimulation targeting the hippocampal-cortical network selectively improved memory precision ($p<0.01$), with no effect on memory success ($p>0.1$). fMRI was used to measure corresponding hippocampal-cortical network changes, and results from these analyses will be discussed. These preliminary findings suggest that memory precision not only necessarily requires the hippocampus and surrounding tissue of the medial temporal lobe, but also critically depends on the hippocampal-cortical network.

Disclosures: A. Nilakantan: None. **D.J. Bridge:** None. **S.A. VanHaerents:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.04/SS31

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R21MH108863

Title: Testing the role of dorsolateral prefrontal cortex in memory-related viewing behaviors using non-invasive stimulation

Authors: *D. R. O'YOUNG[1], D. J. BRIDGE[2], S. A. VANHAERENTS[2], J. L. VOSS[3]
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Abstract: Dorsolateral prefrontal cortex (DLPFC) has been implicated in recollection of episodic memories. The contribution of this region to purely cognitive processing demands of recollection versus memory-related viewing behaviors is not fully understood. To evaluate these

distinct possible DLPFC functions, we applied continuous theta-burst transcranial magnetic stimulation (cTBS) prior to administering an associative recognition test for face-context associations. Eye-movement tracking was used to evaluate memory-related visual search during retrieval. Subjective reports of recall and recognition accuracy were used to evaluate recollection memory. Subjects received either cTBS or sham stimulation prior to the memory test, using a 2-day within-subjects study design with counterbalanced order of cTBS versus sham. cTBS was delivered to a left DLPFC location that has shown increased activity with recollection in this task in a previous study. In a pilot sample with no brain stimulation (N=14), we found that increased viewing of faces correctly paired with a given context occurs with successful recollection within 500-750 ms of stimulus onset (T(13)=2.49, P=.03). In subjects receiving brain stimulation (N=8), significantly increased viewing during this 500-750 ms time period occurred on trials with successful recollection in the cTBS relative to the sham condition (T(7)=2.61, P=.04). No effects of cTBS were observed on overall recollection, recognition accuracy, or basic characteristics of eye movements, such as latency to first facial fixations. This provides the first evidence of changes to memory-related viewing behaviors due to DLPFC stimulation. These findings indicate that left DLPFC contributes to recollection-related viewing behaviors, but not necessarily to the cognitive processes involved in memory retrieval irrespective of viewing behavior.

Disclosures: D.R. O'Young: None. **D.J. Bridge:** None. **S.A. VanHaerents:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Topic: H.02. Human Cognition and Behavior

Support: NIA Grant R01AG049002

NIA Grant T32AG20506

Title: Targeting hippocampal-cortical memory networks in elderly adults using noninvasive brain stimulation

Authors: *J. A. WALKER[1], M. S. HERMILLER[2], A. S. NILAKANTAN[5], M.-M. MESULAM[6], S. WEINTRAUB[7], M. WARD[1], S. A. VANHAERENTS[3], D. J. BRIDGE[4], J. L. VOSS[4]
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Abstract: As one ages, memory declines across multiple domains, including associative memory. There are corresponding declines in functional and structural connectivity between the cortex and the hippocampus, the structure responsible for creating and utilizing associations in episodic memory. Here we examined whether stimulation of a parietal cortex location that is part of the hippocampal network would influence the function of this network in older adults. Elderly adults (N=15; ages 64-81 years) received 20Hz repetitive transcranial magnetic stimulation (rTMS) targeting the hippocampal-cortical network for five consecutive days. They were tested before and one day after stimulation using a memory task that measured object recognition and object-scene associative recollection. Participants learned pairings of objects and scenes during fMRI scanning. Old/new item recognition memory was tested for the objects followed an associative recollection test for the associated scenes. A wealth of previous findings indicates that memory for object-scene locations should be dependent on the hippocampal network to a larger degree than memory for the individual objects, and likewise memory impairments of aging are relatively specific for such associative information. We found that stimulation selectively improved object-scene associative recollection (p=.03), but not object recognition memory. These findings suggest that network-targeted noninvasive stimulation can selectively influence the function of hippocampal memory networks in elderly adults. As this network is disrupted in healthy aging as well as a host of other neurodegenerative disorders such as Alzheimer's Disease, these findings are therefore relevant to the development of non-invasive stimulation interventions for individuals with both healthy age-related and clinical memory impairments.

Disclosures: J.A. Walker: None. **M.S. Hermiller:** None. **A.S. Nilakantan:** None. **M. Mesulam:** None. **S. Weintraub:** None. **M. Ward:** None. **S.A. VanHaerents:** None. **D.J. Bridge:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.06/SS33

Topic: H.02. Human Cognition and Behavior

Support: R01AG049002

R01MH106512

R01MH111790

Title: Evaluating long-term effects of multi-day rTMS in healthy young and elderly adults

Authors: *M. M. GUNLOGSON[1], R. T. PALUMBO[1], J. T. O'NEIL[2], V. MCDONALD[2], S. A. VANHEARENTS[3], J. L. VOSS[1]
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Abstract: Previous studies have shown that repetitive Transcranial Magnetic Stimulation (rTMS) applied for multiple consecutive days targeting the hippocampal-cortical network can increase functional MRI connectivity of the network and improve memory. However, nothing is known about whether multi-day rTMS has long-term effects on cognition or the brain. We analyzed MRI and neuropsychological data from an ongoing study in healthy young adults (n= 11, ages 18-34) and healthy elderly adults (n= 8, ages 66- 82). Assessments were made three times throughout the course of a 10-day rTMS regimen, which included 5 days of suprathreshold rTMS and 5 days of subthreshold (sham) rTMS. The long-term follow-up session was conducted 6.75 months on average (range = 5-8) after completing the rTMS protocol. The rTMS regimen involved 20-Hz stimulation at 100% MT to a left-parietal region defined by high fMRI connectivity with the body of the left hippocampus, and neuropsychological status was assessed using the NIH Toolbox for Cognition. Combined data from young and elderly adults showed small but significant improvement across sessions on the composite cognition score, which is comparable to IQ (P=.0037), reflecting significant increase in performance that was likely due to practice effects. There was marginal increase in scores between baseline and long-term follow-up (P=.0344). Results from a blinded neuroradiological assessment of corresponding structural MRI scans will also be discussed. These results suggest that there are no measurable negative consequences of multi-day rTMS on cognitive status, with trends towards improved cognitive performance following this stimulation regimen coupled with repeated testing sessions.

Disclosures: M.M. Gunlogson: None. **R.T. Palumbo:** None. **J.T. O'Neil:** None. **V. McDonald:** None. **S.A. VanHearents:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.07/SS34

Topic: H.02. Human Cognition and Behavior

Support: NIMH R01-MH106512

Title: Comparison of hippocampal-cortical network modulation by targeted noninvasive stimulation to modulation by memory processing

Authors: *K. N. WARREN[1,2], M. HERMILLER[2], R. PALUMBO[2], S. VANHAERENTS[3], D. BRIDGE[2], J. VOSS[2]

[1]Northwestern Univ. Interdepartmental Neurosci., [2]Med. Social Sciences, Neurology, and Psychiatry, [3]Neurol., Northwestern Univ., Chicago, IL

Abstract: The distributed network of cortical regions functionally correlated with the hippocampus support episodic memory. Previous work indicates that noninvasive brain stimulation targeting the hippocampal-cortical network increases resting-state correlations among network regions and improves associative memory. However, this network can also be altered by cognitive demands, such as engaging in memory. It is therefore unclear the extent to which changes in connectivity during resting-state fMRI due to stimulation reflect network strengthening, versus heightened engagement of cognitive operations related to memory. Here we compare these forms of network modulation using multi-day, noninvasive stimulation of the hippocampal-cortical network and measures of resting-state and autobiographical memory fMRI connectivity. Subjects (N=16) underwent resting-state and active autobiographical-retrieval fMRI scans followed by five consecutive days of high-frequency (20 Hz) repetitive transcranial magnetic stimulation to left lateral parietal cortex. Post-stimulation resting-state and autobiographical-retrieval fMRI followed the last day of stimulation by 24 hours. The site of stimulation was chosen based on subject-specific resting-state correlation with the left hippocampus at baseline. For the stimulation control condition, all sessions were repeated on each subject using subthreshold stimulation at the same location, with order counterbalanced with full-intensity stimulation. Our initial analyses used whole-brain, global-connectedness analyses to identify regions that exhibited different levels of connectedness across resting-state versus autobiographical-state at baseline. This analysis revealed a set of regions with increased connectedness during the autobiographical-state versus during resting-state ($p<0.05$). Hierarchical clustering of connectivity graphs indicated that global connectedness differences were driven by two large, distributed networks ($p<0.001$). One network comprised right-lateralized frontotemporal regions and the other comprised bilateral frontoparietal regions. These robust modulatory effects of autobiographical memory retrieval on connectivity will be used as a benchmark against which to compare the effects of network-targeted brain stimulation. Differences in hippocampal connectivity that occur as a function of noninvasive brain stimulation versus autobiographical retrieval will be discussed, in order to determine the extent to which effects of network-targeted stimulation on hippocampal networks diverge from the modulation via engagement of relevant cognitive demands.

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Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.08/SS35

Topic: H.02. Human Cognition and Behavior

Support: R01MH111790

Title: Dynamic interaction between episodic and motor memory systems

Authors: *J. L. VOSS[1], S. KIM[2]
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Abstract: Neural systems supporting episodic memory and motor memory are known to be distinct with different operational characteristics. Nonetheless, many studies suggest that they compete for limited resources in that motor learning harms consolidation of newly encoded episodic memories, and vice versa. However, little is known regarding how their interactions vary dynamically over the course of learning. We developed a novel fMRI experiment in which subjects performed motor adaptation learning with interleaved object-location association (episodic) learning in order to identify interactions between these two types of learning and corresponding neural correlates. Subjects were presented interleaved learning blocks where a visual feedback of reaching movement was presented or hidden to manipulate motor learning. In healthy young subjects (N = 24, ages: 19-35 years), subsequent memory performance was significantly reduced for object recognition and source memory recollection for blocks with feedback (motor adaptation) versus control (no motor adaptation). The reduction of episodic memory became less significant in later stages of motor learning, as motor performance plateaued. Motor learning was also significantly impaired by the previous encoding of episodic memory. This competition was correlated with reduced activity of bilateral hippocampus and ventromedial prefrontal cortex, associated with the reduction in subsequent episodic memory due to motor learning. The extent of the motor-episodic interference across subjects was significantly related with that of reduced activity in ventromedial prefrontal cortex, suggesting that motor and episodic learning compete for computational resources of this area. These results support bidirectional and dynamic interference between motor and episodic learning and memory systems, potentially reflecting competition for limited encoding resources.

Disclosures: J.L. Voss: None. **S. Kim:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.09/SS36

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH106512

Title: Hippocampal oscillatory signals of memory-related viewing behaviors

Authors: *D. J. BRIDGE[1], J. A. WALKER[1], C. ZELANO[1], N. W. WHITMORE[1], S. A. VANHAERENTS[1], J. L. VOSS[2]
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Abstract: Viewing behaviors measured with eye-movement tracking provide rich information regarding the focus of attention, the content of memory, and specific cognitive processes engaged on a millisecond time scale. We capitalized on this strength by simultaneously acquiring intracranial EEG (iEEG) recordings from the medial temporal lobe of human epilepsy patients to link moment-to-moment behavioral markers of memory processing with moment-to-moment neural recordings from the hippocampus. We aimed to identify hippocampal oscillatory correlates of novelty detection versus retrieval as these processes unfolded over time. Subjects (N=2) completed a multi-phase object-location association task while we recorded eye movements and hippocampal iEEG. During a Study phase, subjects viewed individual objects displayed at different locations on a background scene. In the following Refresh phase, subjects either viewed the objects in their same locations (Match) or viewed the objects in novel locations (Mismatch). On a final Recognition test, subjects saw each object in three locations (original, novel, lure) and were prompted to select the object's original location. During Mismatch Refresh, we time-locked hippocampal iEEG activity to the onset of fixations to each object-location. We identified theta and gamma power increases associated with memory retrieval (viewing the original location), and modest beta and gamma power increases linked to novelty detection (viewing the updated location). Power increases in theta/gamma during retrieval fixations also predicted memory stability, whereas power changes in beta during novelty fixations predicted memory updating, as measured on the final recognition test. This study is the first of its kind to identify distinct hippocampal oscillatory correlates of retrieval versus novelty detection as they occur in rapid succession over brief temporal intervals, showing multiple hippocampal contributions to distinct memory processes with high anatomical and temporal precision.

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Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Topic: H.02. Human Cognition and Behavior

Support: NIA - RO1AGO49002

NIH - 1S10OD020080-01

Title: Brain stimulation of functional networks for associative learning in aging

Authors: *Z. FATIMA[1], T. RAIJ[2], N. SCHNEIDER-GARCES[4], M. S. HERMILLER[3], R. MCINTOSH[5], J. L. VOSS[3]
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Abstract: Previous findings indicate that young adults learn new scene-color pairings via trial-and-error at different rates depending on dynamic functional connectivity measured with magnetoencephalography. Specifically, in fast learners, posterior parietal areas show stronger functional connectivity early in the trial (0-200ms), followed by prefrontal-striatal-medial-temporal connectivity later in the trial (200-600ms). Here, brain stimulation was administered early within trials in older adults with the working hypothesis that stimulation would modulate learning. Twenty-one participants were enrolled in the study and nineteen individuals (mean age: 72 ± 7 years, 12 female) completed both fMRI and rTMS components. Parietal cortex locations that were involved in early learning were identified individually for each participant with fMRI and targeted with high-frequency rTMS (300-ms trains at 20Hz for every trial, total of 672 pulses at 100% motor threshold) during two sessions, active and sham rTMS, separated by a rest period. Not all participants were able to learn associations for all scene-color pairs. Behavioral data were therefore sorted by learning difficulty for each participant (easy and hard, based on accuracy). A negative correlation between age and mean accuracy for easy stimuli was significant for the active condition only ($r = -0.68$, $p<0.005$). To further understand the effect of age on stimulation, the sample was split into two groups based on the mean age. A significant effect ($p<0.005$) for active stimulation in younger versus older adults was found. There was no significant difference between accuracy for sham conditions for the two groups. Younger elderly showed better learning with stimulation compared to sham while older elderly performed worse. Moreover, estimated amplitude of the electric field induced on the cortex by rTMS in older-elderly participants correlated with their performance, with higher intensity associated with impaired performance. Last, we examined patterns of brain-behavior correlations in the fMRI data for easy pairs and found that posterior parietal regions were negatively correlated with performance in older elderly. Our findings suggest that the same stimulation parameters can differentially impact learning and memory systems in elderly of different ages and that parietal networks may play different functional roles depending on age. These results have important ramifications for continued development of non-invasive stimulation methods for memory improvement in aging.

Disclosures: Z. Fatima: None. **T. Raij:** None. **N. Schneider-Garces:** None. **M.S. Hermiller:** None. **R. McIntosh:** None. **J.L. Voss:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.11/SS38

Topic: H.02. Human Cognition and Behavior

Support: NSERC

Title: Memory framework for testing deep brain stimulation, augmenting memory and investigating long term accelerated forgetting in patients with epilepsy

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Abstract: Memory impairment due to neurological disorders, structural damage, epilepsy, and natural aging represents a major health care issue. Few interventions have been shown to improve memory function in the human brain. Deep Brain Stimulation (DBS) is a surgical treatment used for several neurodegenerative diseases, with relatively little unknown about its mechanism of action. Currently the application of DBS to improving memory in humans has met with varied results. Patients with refractory epilepsy provide a unique opportunity to use intracranial electroencephalography (iEEG) to study memory while they perform behavioural tasks. As well, patients with temporal lobe epilepsy are known to have memory related cognitive impairments including accelerated long-term forgetting (ALF). Thus our current research goals are: 1) to create a behavioural task to effectively assess a patients' visual recognition and associative memory; 2) to investigate neural activity that may impact subject performance in short and long-term paradigms, with long term paradigms focusing on ALF; and 3) to assess DBS's effect on memory. Participants who have undergone implantation of iEEG electrode, view scenes with one of two targets embedded in each scene, while collecting iEEG recordings. Participants are asked to identify repeated scenes and their associated target, thus evaluating specific memory processes, including both recognition associative memory in a spatial context believed to be correlated with hippocampal activation. Preliminary results demonstrate above chance correct recognition for scene recollection and slightly above chance accuracy for associated targets. This behavioural framework will also be used to examine neural correlates of behavioural performance within, between subjects and compared against healthy controls. Lastly, it will be used to investigate performance changes as a result of DBS. If successful, DBS may be a viable treatment option for memory problems arising from epilepsy and other neurodegenerative conditions.

Disclosures: C. Katz: None. **V. Barkley:** None. **K.D. Duncan:** None. **T.A. Valiante:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.12/SS39

Topic: H.02. Human Cognition and Behavior

Title: Tuning direct electrical amygdala stimulation parameters for declarative memory enhancement in humans

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Abstract: We have previously demonstrated that brief electrical stimulation to the basolateral amygdala (BLA) reliably enhances memory in humans without eliciting an emotional response. The present study examined whether human amygdala stimulation immediately following the presentation of neutral object images enhanced later declarative memory and the effects of various stimulation parameters on later declarative memory. We recruited 25 epilepsy patients undergoing intracranial EEG (iEEG) with depth electrode contacts placed in the BLA and sub-regions of the medial temporal lobe (MTL). During continuous iEEG, each participant was presented a series of photographs of neutral objects, some of which were followed immediately by stimulation to the amygdala (8 trains of 50-Hz pulses). In further experiments, we manipulated stimulation amplitude (0.5-3.5 mA), duration (1-3 sec), and location (BLA or MTL sub-region) across subsets of patients to determine whether any stimulation parameters might boost the original memory enhancement effect. No epileptiform activity was elicited by the stimulation. Participants reported no awareness of the stimulation for any stimulation condition. Recognition memory for half the images was tested immediately after the study session and for the other half of the images the following day. Free recall memory for all of the images was also measured just before the immediate recognition test. Across all patients and stimulation parameters, participants recognized neutral objects initially followed by amygdala stimulation more accurately than control objects during the one-day test. On the immediate test, participants performed similarly when freely recalling and recognizing previously stimulated versus control objects. Greater stimulation amplitudes and durations produced similar memory enhancement effects to the original stimulation parameters during the one-day test. Stimulating other MTL sub-regions, like the entorhinal cortex, with the same parameters as prior BLA stimulation experiments produced an impairment of memory for stimulation-paired objects. Notably, accurate recognition of stimulated objects elicited oscillatory activity between the BLA, hippocampus, and perirhinal cortex that resembled the prior stimulation pattern. Thus, human amygdala stimulation prioritizes event-specific declarative memories in long-term storage, the

recollection of which is associated with a distinct electrophysiologic signature of prior stimulation. With further tuning, amygdala stimulation may provide a novel therapeutic intervention for memory disorders through selective enhancement of specific memories.

Disclosures: C.S. Inman: None. **J.R. Manns:** None. **K.R. Bijanki:** None. **D.I. Bass:** None. **R.E. Gross:** None. **J.T. Willie:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

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Program#/Poster#: 168.13/SS40

Topic: H.02. Human Cognition and Behavior

Support: NRF of Korea funded by the Ministry of Science, ICT and future Planning (2015R1A2A2A03004026)

Title: Direct electrical stimulation of the human temporal cortex enhances memory

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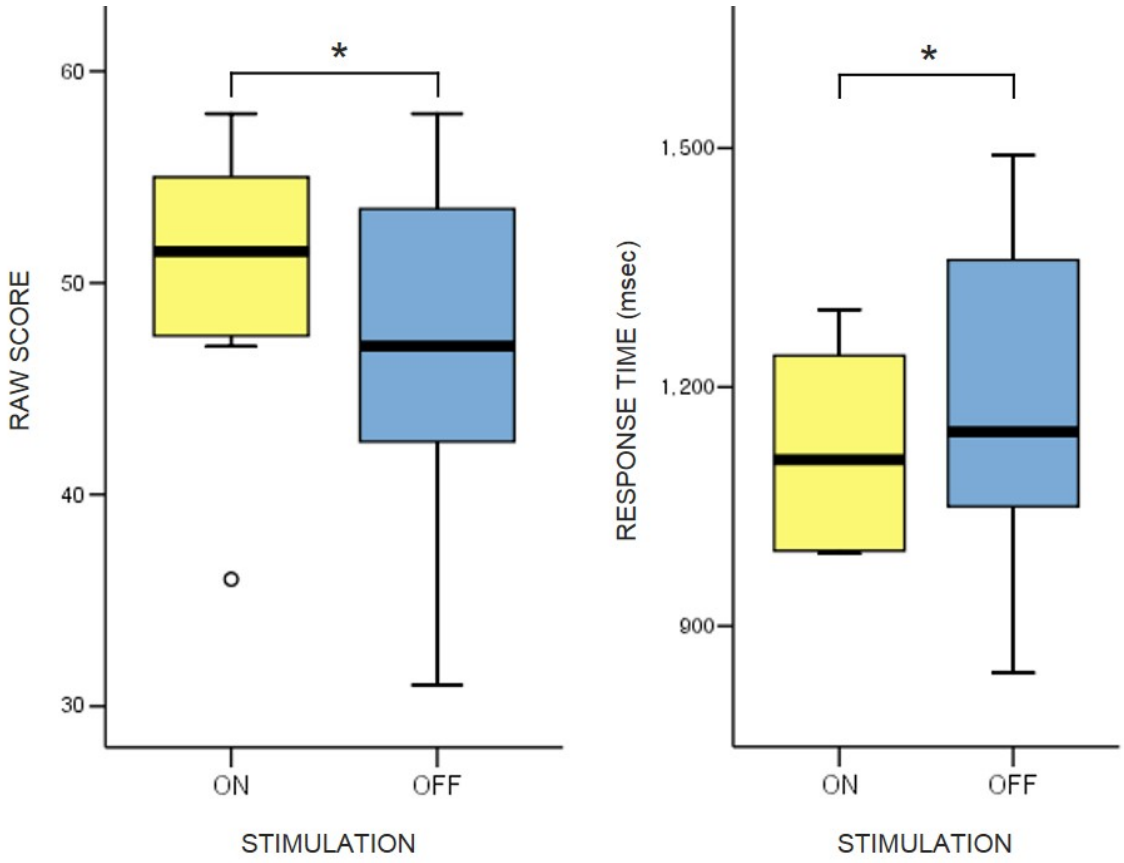
Abstract: The influential notion that the hippocampus with surrounding large-scale brain networks critically support episodic memory formation has not been directly tested in humans. Considerable interest exists to modulate the cortical-hippocampal networks, which might be the putative target of interventional therapy for memory impairment. Previously, with direct hippocampal stimulation, we found functionally interacting cortical regions. In line with the previous work, here we performed electrical stimulation of the cortical region interacting with hippocampus in order to characterize its behavioral effect on memory and changes in network. Here, epilepsy patients with intracranial electrodes performed verbal-episodic memory task. During the encoding phase, subjects received 50 Hz electrical stimulation to the temporal cortex interacting with hippocampus. We analyzed changes in cortico-hippocampal networks and investigated behavioral effect on memory. We found that temporal cortical stimulation changed the activity of the medial temporal lobe regions. Moreover, stimulation enhanced connectivity of the cortical-MTL circuit and concomitantly improved memory performance. Stimulation of the cortex interacting with hippocampus could reciprocally modulate cortical-hippocampal networks, with memory enhancement.



Disclosures: **S. Jun:** None. **J. Kim:** None. **C. Chung:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 168.14/SS41

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

WFBMC Dept. of Neurosurgery

Musk Foundation

OS Fund

Title: Fixing broken memory: Facilitation of delayed recognition short-term memory in human subjects via a neural prosthetic for human memory

Authors: *R. E. HAMPSON[1], B. M. ROEDER[1], A. S. DAKOS[1], R. T. WICKS[1], M. R. WITCHER[1], D. E. COUTURE[1], A. W. LAXTON[1], H. MUNGER-CLARY[1], G. POPLI[1], M. J. SOLLMAN[1], D. SONG[2], B. S. ROBINSON[2], V. Z. MARMARELIS[2], T. W. BERGER[2], S. A. DEADWYLER[1]
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Abstract: Application of a neural prosthetic for human memory requires demonstration that the system is effective at facilitating different types of memory at variable delays. In addition, a neural prosthetic implemented in the hippocampus needs to be tested on memory consistent with hippocampal-dependent delays of minutes to hours, since shorter term memory (seconds) could potentially be processed by neocortical and subcortical circuits. Building on the demonstration by the WFBMC-USC DARPA RAM project team of working memory facilitation within a delayed-match-to-sample (DMS) task, we have tested the same system on delayed recognition memory with delays ranging from 10 to 40 minutes.
Human subjects undergoing Phase II invasive monitoring for intractable epilepsy (as in the adjacent posters by this team) were implanted with macro-micro depth electrodes targeting the hippocampal CA1 and CA3 cell layers. Subjects were initially trained to complete a visual DMS memory task which required the subjects to respond to a Sample image, retain that memory over a delay, then recall the Sample images in the subsequent Match phase of the task. Unlike the prior report (Deadwyler et al., this session), performance on the DMS phase of the test and training was required to be near 100%, therefore delays were limited to 1-10 sec. Similar to the DMS stim testing, a multi-input/multi-output (MIMO) sparse nonlinear model was computed to provide microelectrical stimulation patterns that predicted CA1 neuron firing from real-time CA3 recordings. During the second, stim test, session, subjects received the MIMO model-derived CA1 stimulation during the encoding (Sample) phase for approximately 30% of DMS trials (1-10 sec delays). Following completion of 100 DMS trials, subjects were queried for recall/recognition of Sample images from the task with 10-40 minutes delay from exposure in the DMS task. MIMO stimulation during the DMS task resulted in a 20-30% improvement in Delayed Recognition task performance in four patients, demonstrating that the MIMO model-based stimulation is effective in facilitating human memory at both working memory and short-term memory time frames.

Disclosures: R.E. Hampson: None. **B.M. Roeder:** None. **A.S. Dakos:** None. **R.T. Wicks:** None. **M.R. Witcher:** None. **D.E. Couture:** None. **A.W. Laxton:** None. **H. Munger-Clary:** None. **G. Popli:** None. **M.J. Sollman:** None. **D. Song:** None. **B.S. Robinson:** None. **V.Z. Marmarelis:** None. **T.W. Berger:** None. **S.A. Deadwyler:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

Location: Halls A-C

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Program#/Poster#: 168.15/SS42

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

Title: Fixing broken memory: Measuring human hippocampal dimensions for depth electrode placement in a neural prosthetic for human memory

Authors: *B. M. ROEDER[1], C. WHITLOW[2], A. S. WHITLOW[1], R. T. WICKS[3], M. R. WITCHER[3], D. E. COUTURE[3], A. W. LAXTON[3], H. MUNGER-CLARY[4], G. POPLI[4], M. J. SOLLMAN[4], S. A. DEADWYLER[5], R. E. HAMPSON[5]
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Abstract: Development of a neural prosthetic for human hippocampal-dependent memory requires precise localization of electrode placement within the hippocampal CA1 and CA3 sub-layers. While final localization can be performed with post-surgical MRI and confirmed via neurophysiological recording characteristics, and the initial placement of electrodes at depths appropriate for CA3 and CA1 regions requires measurements of mean and variability of cell layer depth across human subjects. In this study, a morphometric survey of Three-Tesla MRI scans of hippocampus from 100 normal human subjects was conducted to provide average dimensions of the hippocampus along typical implantation tracks. The study was conducted under WFBMC IRB approval on de-identified existing patient data.
Across subjects, the CA1 region was encountered at a depth of 34.31 ± 3.0 mm from the outer table of the skull on the left hemisphere, and 35.64 ± 2.99 mm on the right hemisphere. Notably, the CA1 and CA3 cell fields were separated by a minimum distance of 2.13 ± 0.33 mm on the left and 1.90 ± 0.25 mm on the right, with an maximum outer span from edge to edge of 5.77 ± 1.05 mm on the left and 5.64 ± 1.64 mm on the right. These distances were consistent with probe implantations with the most distal macro (EEG) recording site approximately 45 mm from the outer table of the skull and micro (single unit) recording sites between 33 and 42 mm from the outer table of the skull.
These dimensions were subsequently used to guide implantation of macro-micro depth electrodes (Ad-Tech, Inc., Racine, WI) in thirteen patients undergoing Phase II invasive monitoring for epileptic seizure localization. Electrode site localization within hippocampus was subsequently confirmed via post-surgical MRI, neural firing correlates, and pairwise CA3-to-CA1 cross-correlation to conform that recording sites were in fact localized within the hippocampal CA1 and CA3 cell layers. These results thus provide an important foundation for testing and implementing a neural prosthetic for human memory as shown in the accompanying presentations by WFBMC-USC DARPA RAM Project team at this meeting.

Disclosures: **B.M. Roeder:** None. **C. Whitlow:** None. **A.S. Whitlow:** None. **R.T. Wicks:** None. **M.R. Witcher:** None. **D.E. Couture:** None. **A.W. Laxton:** None. **H. Munger-Clary:** None. **G. Popli:** None. **M.J. Sollman:** None. **S.A. Deadwyler:** None. **R.E. Hampson:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.16/SS43

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

Musk Foundation

OS Fund

Title: Fixing broken memory: Decoding memories from human hippocampal spiking activities

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Abstract: The multi-input, multi-output (MIMO) nonlinear dynamic model used in the hippocampal memory prosthesis predicts and reinstates output signals from input signals without explicitly decoding the memories within those signals. To understand how memories are encoded in the hippocampus, we build memory decoding models to classify visual memories based on hippocampal activities in human. Model inputs are spatio-temporal patterns of spikes recorded in the hippocampal CA3 and CA1 regions of epilepsy patients performing a delayed match-to-sample (DMS) task. Model outputs are 29 non-mutually exclusive binary labels indicating categories and features of sample images. To solve the super high-dimensional estimation problem with short data length, we develop a multi-trial, sparse model estimation method utilizing B-spline basis functions with a large range of temporal resolutions and a regularized logistic classifier. Results show that this model can effectively avoid overfitting and provide significant amount of prediction to memory categories and features using very limited number of data points. Sparse classification function matrices for each label, which represent spatio-temporal characteristics of memory codes, can be reliably estimated with this multi-resolution, multi-trial procedure. These classification models can be used not only to predict memory contents, but also to design optimal stimulation patterns for eliciting specific memories in the hippocampus, and thus have important implications to the development of hippocampal memory prostheses.

Disclosures: X. She: None. **D. Song:** None. **R.E. Hampson:** None. **V. Marmarelis:** None. **S.A. Deadwyler:** None. **T.W. Berger:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

Musk Foundation

OS Fund

Title: Fixing broken memory: Reinstating memory codes with multi-input, multi-output models of the hippocampus in human

Authors: *D. SONG[1], R. E. HAMPSON[2], B. S. ROBINSON[1], X. SHE[1], V. Z. MARMARELIS[1], S. A. DEADWYLER[2], T. W. BERGER[1]
[1]Biomed. Engin., Univ. of Southern California Dept. of Biomed. Engin., Los Angeles, CA; [2]Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Over the past 15 years, we have been working on developing hippocampal prostheses for restoring memory functions lost in diseases or injuries. Different from the traditional deep brain stimulation approach, where non-specific electrical stimulations are used to modulate brain functions, our approach seeks to replicate signal processing properties of brain regions and reinstate neural codes by stimulating the brain with model-based spatio-temporal patterns. To test this approach in human, we have built sparse multi-input, multi-output (MIMO) nonlinear dynamical models of the human hippocampus. Spike trains are recorded from hippocampal CA3 and CA1 regions of epileptic patients performing a variety of memory-dependent delayed match-to-sample (DMS) tasks. Using CA3 and CA1 spike trains as inputs and outputs respectively, sparse generalized Laguerre-Volterra models are estimated with group lasso and local coordinate descent methods to capture the nonlinear dynamics underlying the CA3-CA1 spike train transformations. These models can accurately predict the CA1 spike trains based on the ongoing CA3 spike trains during multiple memory events, e.g., sample presentation, sample response, match presentation and match response, of the DMS task, and has served as the computational basis of human hippocampal memory prostheses. Results have shown that MIMO-based closed-loop stimulation can improve the DMS task performance by 15-25% in five patients, which demonstrates the successful implementation of a memory prosthesis for restoring memory function in human.

Disclosures: D. Song: None. **R.E. Hampson:** None. **B.S. Robinson:** None. **X. She:** None. **V.Z. Marmarelis:** None. **S.A. Deadwyler:** None. **T.W. Berger:** None.

Poster

168. Human Long-Term Memory: Brain Stimulation and Neural Prostheses

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Program#/Poster#: 168.18/SS45

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-C-4016

WFBMC Dept. of Neurosurgery

Musk Foundation

OS Fund

Title: Fixing broken memory: Facilitation of delayed match to sample working memory in human subjects via a neural prosthetic for human memory

Authors: *S. A. DEADWYLER[1], B. M. ROEDER[1], A. S. DAKOS[1], R. T. WICKS[1], M. R. WITCHER[1], D. E. COUTURE[1], A. W. LAXTON[1], H. MUNGER-CLARY[1], G. POPLI[1], M. J. SOLLMAN[1], D. SONG[2], B. S. ROBINSON[2], V. Z. MARMARELIS[2], T. W. BERGER[2], R. E. HAMPSON[1]
[1]Wake Forest Sch. of Med., Winston Salem, NC; [2]USC, Los Angeles, CA

Abstract: Development of a neural prosthetic for human memory requires intervention to correct dysfunctional hippocampal circuitry - i.e. the interconnected neuronal ensembles which organize the CA1 and CA3 subfields into hierarchical networks to process sensory inputs into working memory. Prior investigations by the WFBMC-USC DARPA RAM project team have demonstrated that correct recall of information within a delayed-match-to-sample (DMS) task is contingent upon the robustness of initial encoding of the task stimuli within hippocampus. These studies have yielded a prosthetic system that restored DMS task-related memory in rodents and nonhuman primates, and is now extended to successful memory facilitation in humans.
Human subjects undergoing Phase II invasive monitoring for intractable epilepsy were implanted with macro-micro depth electrodes targeting the hippocampal CA1 and CA3 cell layers. In the initial (training) session, subjects performed a visual DMS memory task in which they remembered screen images during Sample presentation, then recalled those images in the subsequent Match phase of the task after an interposed delay of 1 to 75 sec. Neural recordings from the training session were modeled via a multi-input/multi-output (MIMO) sparse nonlinear model of CA3 and CA1 neuron firing predicted activation of likely connected CA3-to-CA1 cells during Correct Trial performance. During a second (stim test) session, subjects received MIMO model-driven microelectrical stimulation of the CA1 cell layer during the encoding (Sample) phase for approximately 30% of trials within the DMS task. Cognitive task performance on

MIMO stimulated trials was compared with non-stimulated and random pattern-stimulated trials. MIMO stimulation resulted in a 15-25% improvement in DMS task performance in five patients, demonstrating successful implementation of a new neural prosthetic system for the restoration of damaged human memory.

Disclosures: S.A. Deadwyler: None. **B.M. Roeder:** None. **A.S. Dakos:** None. **R.T. Wicks:** None. **M.R. Witcher:** None. **D.E. Couture:** None. **A.W. Laxton:** None. **H. Munger-Clary:** None. **G. Popli:** None. **M.J. Sollman:** None. **D. Song:** None. **B.S. Robinson:** None. **V.Z. Marmarelis:** None. **T.W. Berger:** None. **R.E. Hampson:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.01/SS46

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177

NWO-Vidi 452-12-009

NWO-Research Talent 406-15-291

Title: Coding and recoding of distances in space

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Abstract: While we navigate the world, we form cognitive maps of our environment. It has been shown that these cognitive maps are important to represent distances in familiar environments. Importantly, it is unclear whether these distance representations are based on “navigated” distances and/or on Euclidean distances. “Navigated” distances are based on the length of the route taken between two locations. Euclidean distances are based on how close together two locations are in the environment. Furthermore, it remains unknown if cognitive maps can adapt to changes in the environment, for example when the length of the route between two locations changes. Here, we wanted to probe the nature of distance representations (Euclidean or/and “navigated”) in the brain, especially in the hippocampus. In the same experiment, we tested whether these representations adapt to changes in path length. To this end, we combined fMRI with an extensive navigation paradigm. On day 1 of the experiment, participants had to learn the shortest routes between eight locations while navigating freely through a virtual town. Each of these locations was associated with a different object (object-location task). On day 2

participants had to do the same object-location task. Importantly, on day 2 we manipulated the "navigated" distance by introducing new road blocks, while keeping the Euclidean distance identical to day 1. In addition, we presented all eight objects in a randomized order while collecting fMRI data (object-blocks) on three different time points (data acquisition ongoing). This allowed us to track changes of across-voxel pattern similarity for the different types of object pairs as a function of the Euclidean distance, "navigated" distance and the change in "navigated" distance on day 2. The first object-block was on day 1 before the first object-location task. The second and third object-block were on day 2 before and after the second object-location task, respectively. Preliminary data (n=13) indicate the involvement of the medial temporal lobe and frontal regions in the representation of both, Euclidean and "navigated" distances. Furthermore, the data suggest that changes in path length lead to adaptive remapping of the distance representations in these regions. This study increases our understanding of how the brain represents metrics in space and how flexible these representations are in response to meaningful changes in the environment.

Disclosures: **N. De Haas:** None. **L. Ottink:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.02/SS47

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177

NWO-Vidi 452-12-009

DCN liI 62002195

Title: Mapping and remapping in conceptual space

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Abstract: The idea of a cognitive map was suggested as a mental layout to store causal relationships in the world, and the later discovery of spatially tuned cells such as place and grid cells in rodents made the hippocampal formation the key candidate region for representing a mental map of space. In accordance with the long-known role of the hippocampal formation in a variety of memory-guided behaviors, recent evidence (Constantinescu et al., 2016; Aronov et al., 2017) suggests that spatially tuned cells also support cognitive processes in non-spatial abstract

domains. In addition, human fMRI studies demonstrated another key feature of a cognitive map: The preservation of spatial distances between locations in the hippocampal signal (Morgan et al., 2010; Deuker et al., 2016). Here, we seek to test whether also distances in conceptual space are preserved in the hippocampal code, supporting theories of semantic representation that suggest that conceptual knowledge can be described in a geometric fashion (Gärdenfors, 2004). We probed this idea in a two-day fMRI study in which participants acquired a novel concept which was defined by a 2D stimulus-feature space with the diagonal as category boundary. Participants learned to associate some of the stimuli with objects, placing the objects in certain conceptual distances to each other. We furthermore tracked participants' paths through concept space while they collected objects by editing the feature dimensions of their associated stimuli in order to explore the objects' conceptual context. Finally, we tested whether neural pattern similarity between the objects changes from pre- to post-training object viewing blocks as a function of their distance in concept space. Moreover, in reference to the remapping properties of spatially tuned cells, we probed the dynamics of a potential distance-based representation after systematic changes were introduced to the conceptual space. Behavioral analysis of the learning phase confirms successful acquisition of both concept and associations. Path analysis of the 'navigation' phase reveals more direct (diagonal) paths in later stages of the task, potentially speaking in favor of a map-like conceptual representation. fMRI data of the pre-learning, post-learning, and post-remapping object viewing blocks are currently being analyzed in order to explore neural distance representations. This project might give insight in whether conceptual knowledge is represented in a geometric, map-like manner.

Disclosures: S. Theves: None. **A. Jodzio:** None. **G. Fernandez:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.03/SS48

Topic: H.02. Human Cognition and Behavior

Support: ERC-StG 261177

NWO-Vidi 452-12-009

NWO-Research Talent 406-14-114

Title: Neural signatures of conceptual knowledge acquisition

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Abstract: How does the brain represent newly-acquired knowledge? The hippocampus is known to represent the relation between different events and transform representations of discrete events into higher-order knowledge by abstracting from communalities shared among these events. Recent fMRI studies have reported changes of representational content in medial temporal lobe structures as a result of implicit statistical learning (Schapiro et al., 2012, 2013, 2015), transitive inference (Schlichting et al., 2015) and narrative insight (Milivojevic et al., 2015; Collin et al., 2015). We hypothesized that the hippocampus' ability to abstract information extends to knowledge acquisition, since abstract conceptual knowledge can be learned from regularities across events. Here, we examined the neural dynamics underlying the acquisition of real-world knowledge by assessing changes of neural representations of pseudowords in a Wikipedia concept learning task. Participants were scanned while reading Wikipedia articles about two unfamiliar concepts. To measure knowledge acquisition, we replaced keywords in the original articles with pseudowords. Participants learned the pseudowords' meaning by their semantic embedding in either Wikipedia article. By presenting these same pseudowords in controlled 'pre-' and 'post-learning' scan sessions, we were able to track changes in their neural representation as a function of their semantic relatedness. We found a concept-specific clustering effect in medial temporal and frontal regions, as reflected in a higher increase in pattern similarity for words that were embedded in the same article (i.e. concept), as compared to words from the other article. Analysis of the learning task showed a similar pattern of separation between the two concepts in the medial temporal lobe and frontal cortex, which evolved over time. These findings suggest that the hippocampus is involved, in unison with frontal areas, in representing newly-acquired semantic information by transforming context-specific memories to conceptual knowledge.

Disclosures: L.S. Schurmann: None. **A.R. Backus:** None. **B. Milivojevic:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Support: NWO-Vidi 452-12-009

The Kavli Foundation

The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits

Title: Temporal metric for narrative memory space

Authors: *B. MILIVOJEVIC[1], T. NAVARRO SCHROEDER[2], C. F. DOELLER[1,2]
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Abstract: Internal representation of space and spatial contexts depends on activity of place [1] and grid cells [2] in the hippocampal formation (HF). While firing fields of hippocampal place cells are usually restricted to one particular location within an environment, the entorhinal (EC) grid-cell fields tile the environment as vertices of tessellated equilateral triangles and may act as a metric for space. More recently, cells responsive to time have been reported in the hippocampal formation. Time cells in the hippocampus have similar sparse firing properties in time [3] as place cells do in space, while some EC grid cells have similar repetitive firing profile in time [4] as they do in space. These time cells may therefore provide the mechanism which enables the hippocampal formation to represent temporal context of memories [5]. In our previous research, we have shown that in addition to spatial and temporal context, the hippocampus is also involved in representation of narrative context [6]. In the current study, we examined whether the hippocampal formation, and more widely, the human memory network, also provided a narrative metric. Participants watched a full-length feature film (Sliding Doors) which begun as one narrative but split into two, increasingly diverging, interleaved, 'parallel' storylines which featured the same characters at the same locations. We hypothesized that the hippocampal formation may play a vital role in establishing a narrative metric which may manifest itself in terms of amplitude of oscillatory peaks and troughs in fMRI activity over the course of a narrative. This was indeed the case, with higher amplitude low-frequency oscillations in the HF (EC and hippocampus) than in control region (V1). We discuss these results in terms of a putative role of the HF as a temporal metric for narrative memories.
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[1] O'Keefe & Dostrovsky, 1971. Brain Research 34:171-5. [2] Hafting et al., 2005. Nature 436:801-6. [3] MacDonald et al., 2011. Neuron 71:737-49. [4] Kraus et al., 2015. Neuron 88: 578-589. [5] Eichenbaum, 2014. Nature Reviews Neuroscience 15: 732-44. [6] Milivojevic et al., 2016. Journal of Neuroscience 36: 12412-24.

Disclosures: B. Milivojevic: None. **T. Navarro Schroeder:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.05/SS50

Topic: H.02. Human Cognition and Behavior

Title: Deforming memory space

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Abstract: Entorhinal grid cells are characterized by spatially periodic patterns of activity, with firing fields tiling the entire environment. Models of grid cell firing have focused on the integration of self-motion cues as the origin of this pattern. Therefore, grid cells are thought to provide a metric of space. However, in freely moving rodents, environmental geometry has been shown to exert a strong influence on grid-cell firing patterns. Specifically, firing patterns have been shown to be distorted in highly polarized environments such as a trapezoidal enclosure compared to less polarized environments such as a square. A second stream of research, based on on evidence from rodents and fMRI-studies in humans, suggests a more general role for the entorhinal grid system in representing task-relevant stimulus dimensions beyond spatial navigation; in line with the notion that computations of spatially tuned cells might underlie higher level cognitive functions. Here, we build upon these findings to address the question whether human spatial cognition is influenced by the distortions of the grid pattern observed in highly polarized environments. We employ immersive virtual reality technology to investigate the influence of environmental geometry on human memory. Participants were trained to navigate a trapezoidal and a square arena in which they iteratively learned the positions of objects. Spatial memory was assessed both within and outside the virtual environments via the accuracy of position memory and distance judgments between pairs of locations. Behavioral responses were contrasted between the two arenas based on the deformation patterns observed in grid-cell firing in a trapezoidal compared to a square environment in rodents and exhibited the hypothesized deformations. By speaking to the question whether human memory function is subject to deformations predicted from the distortions of grid-cell firing patterns in highly polarized environments our findings inform our understanding of the role of grid-cell computations in service of cognitive function beyond spatial navigation.

Disclosures: J. Bellmund: None. **T.A. Ruiter:** None. **C. Barry:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Support: H2020-MSCA-IF-2014 661373

Title: Hexadirectional signals during exploration of visual space in human MEG data

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Abstract: Grid cells are one of the core building blocks of navigation and play a pivotal role in memory processes. While single cell recordings in rodents have shown 60° periodic representations of space during spatial navigation (Hafting et al., 2005), studies in non-human primates revealed similar hexagonal firing patterns of cells during image viewing (Killian et al., 2012). Human fMRI studies provide evidence that grid-like signals are also accessible on a macroscopic level (Doeller et al., 2010). The present study set out to investigate grid-like signals during visual exploration in human neuromagnetic activity.
We simultaneously recorded MEG and eye-tracking data from 36 healthy participants during a free viewing encoding task of natural pictures. MEG data were aligned to saccade onsets and source-level gamma power was extracted during saccadic eye movements. One half of the data was used to estimate the potential grid orientation, applying a quadrature filter approach. In the remaining data, trials aligned to the main grid axis were compared to misaligned trials. We found significantly higher 60° periodic gamma power for aligned versus misaligned trials in the anterior part of the medial temporal lobe. Importantly, control analyses (45° and 90° periodicities) did not show this effect, and the 60° periodic gamma power modulation could also not be explained by oculomotor activity.
Our findings show, for the first time, grid-like activity during visual exploration in human neuromagnetic signals. Converging with findings in non-human primates, this speaks to a generalization of hexadirectional signals during spatial navigation to grid-like representations of visual space.

Disclosures: T. Staudigl: None. **O. Jensen:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Support: NWO-Vidi 452-12-009

The Kavli Foundation

The Egil and Pauline Braathen and Fred Kavli Centre for Cortical Microcircuits

Title: Electromagnetic dynamics of hexadirectional activity during virtual navigation

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Abstract: Entorhinal grid cells in rodents fire in a spatially periodic hexagonal pattern and have been suggested as the neural basis of a cognitive map [1-3]. The orientation of the grid map is relatively stable across cells of a given animal, but in environments with polarised geometry preferred grid orientations are even shared between individuals [4,5]. The precise function of grid cells remains unknown, but the role of environmental geometry could provide important clues regarding the underlying computations. Previously, we used free-navigation tasks in virtual reality with functional magnetic resonance imaging (fMRI) in humans to measure hexadirectional activity modulations in the entorhinal cortex as a putative proxy for grid-cell population activity. Hexadirectional signal modulations have been found outside the entorhinal cortex in a wide-spread memory network including medial prefrontal areas [6,7]. In polarised environments, we repeatedly found [8] preferred orientations of hexadirectional activity that were shared between individual participants. However, these findings were restricted to the slow fMRI BOLD signal at a temporal resolution on the order of seconds. Here, we aimed at characterising the fast dynamics of hexadirectional activity modulations using magnetoencephalography (MEG). Based on our previous fMRI results, we predicted hexadirectional signal modulations anchored to the geometry of a polarised environment. Preliminary results on the sensor level show increased spectral power during movements aligned with the a-priori defined, hexadirectional orientations. These findings provide important clues regarding the neurophysiological basis of the fMRI-based hexadirectional signal and its functional role in navigation.
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[2] Moser et al. (2014) Grid cells and cortical representation. Nat Rev Neurosci:1-16.
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[8] Navarro Schröder et al. (2016) Entorhinal processing of reference points. Society for Neuroscience - Annual Meeting.

Disclosures: T. Navarro Schroeder: None. **T. Staudigl:** None. **J. Schoffelen:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

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Program#/Poster#: 169.08/SS53

Topic: H.02. Human Cognition and Behavior

Title: Visual space in human entorhinal cortex

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Abstract: Grid cells in the entorhinal cortex (EC) exhibit place-modulated firing patterns that represent self-location. These firing patterns are six-fold rotational symmetrical (hexadirectional) and were implicated in representing a map of space. Investigations in non-human primates showed that EC neurons further encode eye movement direction and visual space that has not been visited by the animal. In humans, functional magnetic resonance imaging (fMRI) has demonstrated EC activity to depend on virtual running direction in a hexadirectional manner and hence resembles grid cell firing. However, little is known about whether human EC codes for visual space and eye movements as it does in non-human primates. To address this question, we used fMRI to examine human EC responses during a visual tracking- and object location memory task. Participants oversaw a virtual arena from two different bird's-eye perspectives and memorized cue locations while fixating at a moving fixation target. This allowed us to highly control spatial and directional sampling of eye movements while ensuring attentional focus on the spatial layout of the environment. During this task, fixation accuracy was monitored with eye tracking. Subsequently, participants freely navigated the virtual environment in first person perspective and reported the previously learned cue locations by navigating to them. Imaging data was analyzed with respect to eye movement direction and examined for directional modulation of EC activity. To this end, we estimated the set of eye movement directions modulo 60 degrees that maximally drove responses in EC and tested it on independent data. Our preliminary results suggest that human EC activity is indeed modulated by eye movement direction in a hexadirectional manner. These results point towards a shared mechanism for the encoding of navigational and visual space in humans and shed new light on the flexible and dynamic nature of spatial processing in the EC.

Disclosures: **M. Nau:** None. **T. Navarro Schröder:** None. **C.F. Doeller:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Support: NWO-Vidi 452-12-009

ERC-StG 261177

Title: Preactivation of choice options while anticipating future events

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Abstract: The neural dynamics after learning are an important aspect of memory formation. Place cell recordings in rats showed reactivation, or 'replay', of visited locations in an environment during subsequent rest periods. This is suggested to support consolidation and future behavior. Also human fMRI studies have shown evidence for reactivation of memories after initial encoding during subsequent sleep or rest. More recently, it has been shown with place cell recordings that rats also pre-activate, or 'preplay', goal-related unvisited portions of the environment. Preplay has been proposed to also underlie anticipation of upcoming events but empirical support for this assertion remains elusive. Our fMRI study is aimed to test whether the human brain uses a mechanism equivalent to preplay when anticipating future events, and how this relates to subsequent replay and episodic choices. We presented participants with short videos of animated events in the MRI scanner. Each of these events had two alternative options of how the event could end. However, the start of these two alternative options was the same. Participants were presented with these events using the following trial structure: [1] seeing the start of an event, [2] short rest period, [3] giving a verbal response of how the event will most likely continue, [4] seeing the two alternative event options, [5] choosing one of these two event options, [6] getting feedback on this choice (correct/incorrect), and [7] a second short rest period. We hypothesize preactivation of the event options in the rest period preceding the participants' choice, with subtle differences in pre-activation between the subsequently chosen and not chosen event option. Additionally, we hypothesize hippocampal reactivation of only the correct event option in the second rest periods. Furthermore, we will investigate functional connectivity between hippocampus and other regions within the temporal cortex, separately for chosen and not chosen event options and for correct and incorrect event options. Preliminary analyses indicate hippocampal preactivation of both alternative event options in the rest period preceding

the participants' choice. With this study we aim to unravel how humans anticipate to future experiences, and how this relates to their subsequent behavior.

Disclosures: S.H. Collin: None. **C. van Dun:** None. **B. Milivojevic:** None. **C.F. Doeller:** None.

Poster

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Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 16H01503

JSPS KAKENHI Grant Number 17H05947

Title: Interacting mechanisms between the ventral striatum and hippocampus during the encoding of social memories associated with a victory in a competition with others

Authors: *H. SUGIMOTO, T. TSUKIURA
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Abstract: Affective feelings are generated by social interactions with others. Previous studies have reported that the reward-related regions such as the ventral striatum (VS) and medial orbitofrontal cortex (mOFC) contribute to the processing of rewards in a social context as well as monetary rewards. However, little is known about the neural mechanisms underlying memory associated with the winning in a competition with others. The present fMRI study investigated neural activation during the encoding of unfamiliar faces which corresponded to opponents in a game of competition. In this study, 37 right-handed and college-aged healthy participants were recruited from the Kyoto University community. During encoding with fMRI, participants were presented with unfamiliar faces, and were required to play a rock-paper-scissors game with opponents shown by each face. The outcome of Win, Draw or Lose in the game was fed back to participants by showing facial expressions of the opponents. If the opponents showed an angry expression in their losing, the outcome of competition was regarded as Win for the participants. In contrast, a happy face of the opponents was judged as the outcome of Lose. In the outcome of Draw, neutral faces were presented. During retrieval without fMRI, participants were randomly presented with previously learned and new faces, and were required to make old/new judgments for each face. All encoding trials except error responses were categorized into subsequently remembered (Hit) and forgotten (Miss) trials, and the Hit and Miss trials were subdivided by encoding condition (Win, Draw, Lose). In behavioral data, hit rates were significantly higher in Win than in Draw and Lose. In fMRI data, an ANOVA with factors of subsequent memory (Hit,

Miss) and encoding condition (Win, Draw, Lose) revealed that activation in the VS reflected a significant main effect of encoding condition, in which the activation was greater in Win than in Draw and Lose. In addition, the PPI analysis as a seed of the hippocampus, whose activation was associated with the successful encoding (Hit vs. Miss), demonstrated that functional connectivity with the hippocampus modulated by individual hit rates in Win was significantly identified in the VS and mOFC, whereas the same pattern of functional connectivity correlated with hit rates in Lose was found only in the mOFC. In Draw, such functional connectivity was not shown in any regions. These findings suggest that interactions between the reward-related VS and memory-related hippocampus could contribute to the enhancement of memory for emotionally positive events induced by social interaction such as a victory in the competition with others.

Disclosures: H. Sugimoto: None. **T. Tsukiura:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

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Title: Inter-subject synchrony predicts learning success for educational content

Authors: *S. S. COHEN[1], G. TOUCHAN[2], D. ROBLES[2], S. FERRARI[2], S. HENIN[2], L. C. PARRA[3]
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Abstract: Although student engagement is correlated with academic success, the mechanism by which this attentional focus translates into improved performance is unknown. We hypothesized that the level of neural reliability evoked by educational stimuli, measured via the inter-subject correlation (ISC) of electroencephalography (EEG), would predict both attention to and retention of the stimuli. To assess this, the knowledge base of 20 subjects was assessed before and after exposure to educational videos. The reliability of each individual's evoked responses, recorded while watching the videos, was compared to their peers to establish a metric for their relative attentional engagement with the stimuli. Neural reliability correlated with an improvement on test scores after exposure to the educational videos. ISC could also discriminate the attentional state of subjects with perfect accuracy. This suggests that ISC is a marker of the stimulus-related attentional mechanisms necessary to achieve comprehension. In the future, ISC may be used as a metric when designing and assessing educational content and presentation style.

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Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Title: Administration of a beta-adrenoceptor antagonist to block action-induced episodic memory enhancement

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Abstract: We have recently discovered that voluntary movement (a Go-NoGo task, via button press indicated by contextual cues) can enhance memory encoding, and that this action-induced memory enhancement is associated with increased Locus Coeruleus activity. If action-induced memory enhancement is mediated by the noradrenergic system, this suggests that administration of a non-selective central β-adrenergic antagonist (propranolol) will block this enhancement. Therefore, we performed a two-day pharmacological experiment with a total of 32 healthy volunteers (16 females and 16 males) randomly assigned to one of two conditions (Placebo or Propranolol) in a double-blind procedure. During day 1, once participants arrived at the hospital, ECG (electrocardiogram) and BP (blood pressure) were taken. Once the measurements were taken, participants were administered propranolol (40) mg or placebo orally. After 90 min, BP was measured, showing a significance difference in systolic BP between both groups ($p< 0.001$), which indicates that the pharmacological treatment had exerted a hypotensive effect. Then, participants performed the “Go-NoGo” computer task consisting of two phases. During the encoding phase, participants had to press a button (“Go” trials) when the images (68 gray-scale photographs of objects) were presented with a particular colored frame (yellow or blue), or withhold movement (“NoGo” trials). On day 2, BP was again measured and was not different between groups ($p>0.05$), Participants then performed a surprise recognition memory task. A total of 136 images (the 68 that were presented at the time of encoding and 68 new “foils”) were presented in randomized order on a black background (i.e. without a colored frame). Participants were required to indicate whether they remembered (R), were familiar with (K) or did not remember (forgotten, F) the images. We did not, however, observe action-induced memory enhancement (Go vs NoGo) in the placebo group [$t_{(14)}$=-0.005, $p= 0.996$]. Indeed, there was no

group (placebo vs propranolol) main effect at recognition memory testing (Go vs NoGo) [$F_{(1,27)}$= 0.12; p= 0.74]. We hypothesized that differences in systolic BP, a measure of sympathetic tone, may contribute to these memory effects. Nevertheless, we observed a significant linear correlation (r =0.38; p =0.042) between systolic BP and memory score ("Go minus NoGo" correct remember) collapsing across treatment groups. Therefore, the specific memory effects for the "Go" condition can be accounted for by the BP, but without a specific effect of the treatment condition.

Disclosures: A.I. Galarza Vallejo: None. **M. Yebra:** None. **V. Soto-León:** None. **A. Oliviero:** None. **B.A. Strange:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.13/SS58

Topic: H.02. Human Cognition and Behavior

Title: Neural representation of musical contexts in high-level cortical regions

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Abstract: Naturalistic stimuli, such as movies and audio narratives, have been shown to elicit representations in high-level cortical regions (e.g., the posterior medial cortical network: Ranganath & Ritchey, 2012) that code for abstract features of the current situation. These neural representations have the following properties: They are stable within events and vary across events, changing abruptly at moments corresponding to human annotations of event boundaries (Baldassano et al., 2016); they code for features of specific events, e.g., characters in a story (Chen et al., 2017); and these event-specific codes are shared across participants, supporting cross-participant decoding (Chen et al., 2017; Zadbood et al., 2017). Here, we investigate whether these properties extend to musical stimuli. Specifically, we investigate whether individual songs in a long "playlist" of songs are represented in high-level areas in a manner analogous to scenes or events in a narrative. If this is true, we would expect neural patterns in high-level cortical regions to be stable within songs and to change abruptly at song boundaries; the neural patterns in these regions should code for the features of specific songs and also higher-level features such as musical genre; and the representations should be shared across participants, supporting cross-participant decoding of song identity and also genre. The stimuli used were 16 songs distributed equally between two genres (jazz and classical). Participants were required to listen to these 16 songs for two days prior to a third day of listening in an fMRI scanner. During the scanning session, participants listened to the set of 16 songs twice in random order. To analyze the data, we use a representational similarity analysis (RSA) searchlight and also newly

developed Hidden Markov Model methods (Baldassano et al., 2016) to look for representation of high-level features (songs, genres) and also lower-level auditory features. Analyses are ongoing but preliminary results indicate strong representation of song identity in the posterior medial network.

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Poster

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Topic: H.02. Human Cognition and Behavior

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ONR N00014-15-1-2790

Title: Preparatory attentional control state influences later memory

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Abstract: Attentional lapses are pervasive and can contribute to later memory failures. Furthermore, numerous psychiatric and neurological disorders are characterized by deficits in attentional control. Neural fluctuations, both before and after stimulus presentation, predict upcoming working memory and long-term memory performance. We designed a study to test whether fluctuations of attentional control influence subsequent memory encoding. We hypothesized that greater preparatory attentional control would predict better memory. On each trial, participants encoded the locations of four trial-unique objects that appeared simultaneously. Prior to stimulus presentation, a peripheral cue indicated the position of one of the objects. Throughout a blank pre-encoding delay interval, participants maintained covert attention towards the cued location. Then, trial-unique objects were briefly presented at the cued location as well as other, uncued locations. After a blank post-encoding retention interval, one of the objects was centrally presented for a memory test. Participants were asked to report by clicking that object's location. The tested item was either the object that had been cued (valid trials, 75%) or a different object (invalid trials, 25%). We predicted that the pre-stimulus attentional manipulation would influence memory encoding success. Memory performance was assessed using response error, the angular difference between the reported and presented locations. Following valid (vs. invalid) cues, working memory performance was better, as reflected in lower standard deviation in response error. At the end of a block of trials, participants completed long-term recognition

and source memory tests. Participants were presented objects that had been either cued or tested ("old") along with novel lure objects ("new") and rated their confidence that the object had appeared previously. For all old objects, participants also reported their memory for its presented location. Although memory performance was weaker overall, cue validity still predicted response accuracy. Throughout the experiment, electroencephalography (EEG) was recorded in order to have time-resolved neural signatures of attentional control. These results are consistent with neural fluctuations, both before and after encoding, that track attentional control and reflect a major contributor to failures in immediate and delayed memory tests. Altogether, these results suggest that preparatory attentional control reflects a key moment in memory formation.

Disclosures: M.T. deBettencourt: None. **E. Awh:** None. **E.K. Vogel:** None.

Poster

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Support: NINDS IRP

Title: Recognition of attended words is differentially represented in the anterior temporal lobe and the prefrontal cortex

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Abstract: Selective attention can improve memory encoding. In our verbal recognition memory task, recognition performance is better, and reaction times are faster, for words that are preceded by an attention cue than for non-cued words (hereby referred to as attended vs unattended words). Based on intracranial EEG recordings in epilepsy patients performing this task, we previously reported that high-frequency activity in the anterior temporal and prefrontal lobe is involved in attention-enhanced encoding of words (Wittig et al., SfN abstract 2016 & 2017). Here we examine the response of these two areas during the recognition phase of the task, as participants report whether or not they have seen presented words.
We found that both anterior temporal and lateral prefrontal responses separated correctly recognized words from non-recognized words, but the response characteristics were different. In the anterior temporal lobe, high-frequency power was significantly greater for recognized than non-recognized words during word presentation. Prefrontal high-frequency power also significantly increased during correctly recognized words, but power remained elevated until the

response was made.
Next, we found that the anterior temporal lobe distinguished attended vs unattended words that were correctly recognized, whereas the prefrontal cortex did not. In the prefrontal cortex, high-frequency power was indistinguishable for attended vs unattended words, indicating a binary representation of the choice outcome. In the anterior temporal lobe, high-frequency power during unattended words (that were correctly recognized) was lower than that of attended words that were correctly recognized, but higher than that of attended words that were not correctly recognized, indicating a more graded representation of memory strength.
Finally, we compared the physiological response to novel words vs previously seen words. In the anterior temporal lobe, the response to correctly identified novel words was similar to that of correctly recognized unattended words, and thus appears to reflect the memory confidence. In contrast, in the prefrontal cortex the response to novel words was similar to that of non-recognized words, and thus likely reflects the choice outcome.
Consistent with previous reports, our data indicate that both the anterior temporal lobe and prefrontal cortex are involved in recognition memory. Here we reveal distinct contributions of these two regions, with the anterior temporal lobe representing graded memory confidence, and the prefrontal cortex representing binary familiarity judgements related to the decision outcome.

Disclosures: **T. Bonnevie:** None. **J.H. Wittig:** None. **K.A. Zaghloul:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.16/SS61

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Human anterior temporal lobe controls top-down attention to improve verbal memory

Authors: *J. H. WITTIG, JR[1], S. INATI[1], K. A. ZAGHLOUL[2]
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Abstract: Selective attention focuses our mental resources on information relevant to our behavioral goals (Chun et al. 2011). Most often selective attention is studied in the context of visual perception (Maunsell 2015), but selective attention also critically affects what we remember (Chun & Johnson 2011). In visual perception, mechanisms of selective attention have been described for spiking neurons in macaque V1, V4 and MT, where attention enhances visual responses by increasing spike rate, decreasing fanofactor, and decreasing noise correlations (e.g., Cohen and Maunsell 2009). These attentional mechanisms are activated by top-down attentional

control regions in the frontal and parietal cortices (e.g., Moore and Armstrong 2003). These same control regions are also active during episodic memory formation (Uncapher et al 2011) though their target(s) are largely unknown, in part because episodic memory studies rarely control for both attentional state and successful memory formation. Here we present a novel memory task that independently controls for attention and memory processes. Using this task, combined with intracranial EEG and single unit recordings in human neurosurgery patients, we identify a locus and mechanism for attentional-enhancement of verbal memory in the human anterior temporal lobe. In this brain region, an overt preparatory cue leads to suppression of background activity before a to-be-remembered word is read. This decrease in background activity is observed across a population of spiking neurons and manifests as a decrease in high frequency power measured by subdural electrodes. Neurons exhibiting spike-rate suppression also exhibit improved signal-to-noise, as measured by a decrease in fanofactor. However, attention does not affect noise correlations among the population of recorded neurons. Surgically removing the anterior temporal lobe impairs attention-enhanced memory, but has no effect on memorization without selective attention. The observed suppression of background activity enhances memory fidelity by increasing signal-to-noise as verbal stimuli are processed and encoded into episodic memory. Collectively, these results implicate the anterior temporal lobe as a novel and unique attentional-control area that signals preparation for enhanced memorization.

Disclosures: **J.H. Wittig:** None. **S. Inati:** None. **K.A. Zaghloul:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.17/DP12/SS62 (Dynamic Poster)

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Traveling waves in the human cortex are ubiquitous

Authors: *V. SREEKUMAR[1], K. A. ZAGHLOUL[2]
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Abstract: Recent studies have quantified the emergent spatiotemporal patterns of population neuronal activity in the primate cortex during rest. Here, we draw upon the physics of wave propagation to characterize the spatiotemporal organization of activity in the human cortex during memory encoding and retrieval. Nine patients with medically refractive epilepsy engaged in a paired associates task. We examined the instantaneous phase of bandpass filtered LFP signals during encoding and retrieval trials at each site on a grid of electrodes implanted on the

cortical surface. We calculated phase velocity fields to capture changes in the spatial organization of activity across time and detected both plane waves and synchronous waves. The preferred axis of propagation of plane waves was superior posterior - inferior anterior. Beta-band and theta-band plane wave velocities were significantly different, supporting a weakly-coupled oscillator model of propagating waves. Though preliminary analyses found no relation between plane waves and memory performance, the presence of traveling waves was ubiquitous, making up ~45% of the analyzed epochs.

Disclosures: V. Sreekumar: None. **K.A. Zaghloul:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.18/SS63

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Decreases in spectral power and flattening of spectral slope, across time scales, correlate with improved performance during a paired associates memory task

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Abstract: Low frequency (<10 Hz) power fluctuations, particularly in the medial temporal lobe, have been identified as critical elements of the subsequent memory effect. There is however conflicting evidence on whether increases or decreases in low frequency bands are related to successful memory formation (Hanslmayr et al. 2014). Here, we explore the role of theta (3-7 Hz) band power as well as broadband (10-100 Hz) spectral slope, during a paired associates memory task across a cohort (n=43) of subjects implanted with intracranial electrodes (ECoG). Subjects were presented with lists of word pairs of common nouns and were instructed to remember them for subsequent cued retrieval by imagining the two objects together. Intracranial recordings taken during this task were spectrally decomposed and power was compared between subsequently remembered and subsequently forgotten word pairs. We identified robust decreases in low frequency power in both anterior temporal lobes and a flattening of the spectral slope in the left anterior temporal lobe and left inferior prefrontal cortex for subsequently remembered items. This supports the findings of others studying semantic memory. In addition to looking at average changes across subjects, we also explored how baseline power and power fluctuations differed across subjects. As on the item level, we found that decreases in theta band power and a flattening of the power spectral density across the cortex both correlated with improved

performance in a scale free manner across the level of subjects and sessions. This suggests that there is meaningful signal in time scales beyond those explored in typical trial level analysis and that these patterns may explain some of the heterogeneity we observe across subjects.

Disclosures: T. Sheehan: None. **V. Sreekumar:** None. **K.A. Zaghloul:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.19/SS64

Topic: H.02. Human Cognition and Behavior

Support: NINDS IRP

Title: Decoding the dynamic neural representation of specific stimuli in human associative mrmory

Authors: *M. TROTTA[1], J. H. WITTIG, JR[2], K. A. ZAGHLOUL[3]
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Abstract: Decoding the neural representation of specific stimuli has long been considered an important step towards understanding human memory and semantic processing, and recent results in scalp and intracranial EEG have shown exciting results towards this goal. We were specifically interested in exploring the dynamic nature of associative memory by studying the formation, reinforcement, and remapping of word associations. Electrocorticography (ECoG) and intracranial single-unit recordings were collected from epilepsy patients with surgically implanted monitoring electrodes. Participants (n=18) were given a visual paired-associates word task in which they were asked to learn associations between specific word pairs. By using high trial counts with a small word pool and by systematically permuting the association pairs, we were able to study the process of learning and relearning of associations. We used established methods of machine learning and high-dimensional similarity to classify distinct word pairs using frequency-filtered signal bands from electrodes distributed primarily across the temporal and frontal lobes. Our results from ECoG and single-unit recordings support existing evidence that stimuli-specific neural representations are spatially distributed across individual neurons and cortical regions. While previous studies have focused on either the lexico-semantic neural response to stimuli or the temporal context reinstatement during retrieval, in this work we were interested in the relative contribution of each of these elements to the overall response. We found that although the neural representation of an association is partly related to semantic meaning of each word, the response is more significantly comprised of a representation unique to the pair of words.

Disclosures: **M. Trotta:** None. **J.H. Wittig:** None. **K.A. Zaghloul:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.20/SS65

Topic: H.02. Human Cognition and Behavior

Support: John Templeton Foundation

Title: Hold that thought: When mental contexts survive interruptions to bind memories

Authors: *S. DUBROW, *S. DUBROW, M. SONG, Y. NIV, K. NORMAN
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Abstract: Our daily lives are filled with brief interruptions that can pull our train of thought away from our current goal. Context change accounts of memory suggest that each of these interruptions segment our experience and induce separation in memory (Polyn et al, 2009; Zacks et al, 2007). Indeed, there is a great deal of evidence consistent with this account (e.g., Ezzyat & Davachi, 2011; DuBrow & Davachi, 2013; Sahakyan & Smith, 2014; Lositsky et al, 2016). However, we do not always lose our train of thought when encountering an interruption, and recent work has shown that prior contexts can sometimes persist across changes to cluster memories together (Chan et al, 2017). Thus, an outstanding question is what allows prior context to persist across interruptions in some cases but not in others. Here, we investigated whether the degree of conflict experienced when encountering an interruption mediates the extent to which prior contexts can persist. We ran a series of studies on Amazon's Mechanical Turk (N = 225) in which we presented participants with sequences of scenes that were occasionally interrupted with faces. Because the scene task was dominant, we predicted that the scene context could persist across the short face interruptions. For half of the participants, we induced response conflict by presenting each face with a scene in the background. In order to make the face responses correctly, participants would have to ignore the scenes because the correct response for the scene might conflict with the correct response for the face. We predicted that in the conflict condition, face interruptions would be accompanied by scene context suppression, which would induce bigger context shifts and create segmentation in memory. We used recognition priming to assess whether memory judgments on faces were facilitated by exposure to the scenes that preceded them. More segmentation should reduce this recognition priming effect. Indeed, across three studies, we found significantly more recognition priming of faces by scenes in the control conditions than in the conflict conditions. This suggests that the dominant scene context can persist across interruptions when that context does not interfere with the current task. In an ongoing fMRI study, we are developing methods to track simultaneous mental contexts

noncompetitively. We will use those methods to track the extent to which neural measures of context persistence predict associative memory and how they are modulated by conflict.

Disclosures: S. Dubrow: None. **M. Song:** None. **Y. Niv:** None. **K. Norman:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.21/SS66

Topic: H.02. Human Cognition and Behavior

Support: F32 NS096962

Title: Intentional forgetting via memory weakening in sensory cortex

Authors: *T. H. WANG[1], K. PLACEK[2], J. A. LEWIS-PEACOCK[3]
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Abstract: Forgetting is often thought of as a passive process - a failure of memory - but can be understood as an adaptive, active, and often automatic process of curating memories. It can also be deliberate: the intention to forget can produce long-lasting forgetting. How does the brain accomplish this? Two successful strategies have been identified with distinct neural signatures: “direct suppression” attempts to squash the memory by engaging prefrontal control regions to inhibit processing in the hippocampus, whereas “thought substitution” attempts to replace the memory with alternatives from long-term memory through enhanced hippocampal engagement (Benoit and Anderson, 2012). Here, we explored whether a memory weakening mechanism that contributes to unintentional forgetting - in which moderately active memories get weakened via local inhibition through a process of oscillating inhibition in the brain regions supporting their representation (Lewis-Peacock & Norman, 2014) - is also active during deliberate forgetting. We hypothesized that the intentional forgetting of visual memories is supported, in part, by the promotion of moderate activation of those memories in visual brain regions. In an item-method directed forgetting experiment, we used multivariate pattern analysis (MVPA) of fMRI data to quantify the strength of processing of memory items in ventral temporal cortex following ‘remember’ and ‘forget’ instructions. Our results revealed that the intention to forget an item led to stronger processing of that item in sensory cortex compared to trials with a remember intention. Consistent with our hypothesis, this produced a reliable nonmonotonic U-shaped relationship between neural activation and memory performance such that moderate activity of to-be-forgotten items was predictive of successful forgetting of those items. Furthermore, functional connectivity analyses revealed a stronger coupling between dorsal lateral prefrontal cortex (DLPFC) and hippocampus, suggesting processes involving cognitive control on memory

were coactive with stronger processing in sensory cortex during intentional forgetting. These results suggest that sensory cortex may play a larger role in forgetting than previously appreciated.

Citations:
Benoit, R.G. and Anderson, M.C.(2012). Two neural mechanisms of voluntary forgetting. Neuron. 76: 450-460. Lewis-Peacock, J.A. and Norman, K.A. (2014). Competition between items in working memory leads to forgetting. Nat. Commun. 18;5:5768.

Disclosures: T.H. Wang: None. **K. Placek:** None. **J.A. Lewis-Peacock:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

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Program#/Poster#: 169.22/TT1

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH63901

NIH Grant MH106280

Title: Large-scale network connectivity changes underlying memory formation

Authors: *A. TAMBINI[1], D. J. LURIE[2], R. C. LAPATE[1], M. D'ESPOSITO[1]
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Abstract: It is well-established that individual brain regions show differences in activity during initial memory encoding that is related to later memory retrieval. Past work has also shown that connectivity between specific brain regions is predictive of successful encoding (e.g. hippocampal connectivity, Ranganath et al., 2005). However, despite recent work showing that retrieval from long-term memory involves a reconfiguration of large-scale network connectivity structure (e.g. Fornito et al., 2012), and that specific brain regions play an important role in this process (e.g. Geib et al., 2015), it is currently unclear whether successful encoding is similarly associated with large-scale connectivity changes evident at the level of whole-brain networks and their modular structure. Here, we asked whether the encoding of associations and items into long-term memory is associated with changes in the structure of large-scale network connectivity. To do so, we applied graph-theoretical analyses to BOLD fMRI data while participants incidentally encoded stimulus pairs and their memory was tested after scanning. We parcellated the brain into regions based on 17 large-scale cortical networks (e.g. modules) previously defined by Yeo et al. (2011) and supplemented this parcellation with sub-cortical regions. Correlation matrices were estimated for distinct memory conditions (associative hits,

associative misses/item hits, and item misses), which allowed us to examine whether within versus between module connectivity for individual sub-networks varied based on later memory. At the level of the entire network, dissociable connectivity patterns were found for successful associative memory (associative hits vs. misses) as well as for successful item memory (item hits vs. misses). Associative encoding was associated with a decrease of between-module versus within-module connectivity (measured by the participation coefficient) for the medial temporal subsystem of the default mode network and visual networks. Greater within-module connectivity during successful versus unsuccessful associative encoding in the medial temporal subsystem was also related to better associative memory across participants. In contrast, successful item encoding was associated with a more integrated and less modular network structure at the level of the whole brain, with a broad increase in across-module interactions. These findings provide novel evidence that successful encoding is associated with changes in large-scale brain network structure, highlighting the role of local versus global connectivity of medial temporal regions during associative memory encoding.

Disclosures: **A. Tambini:** None. **D.J. Lurie:** None. **R.C. Lapate:** None. **M. D'Esposito:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.23/TT2

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R15AG052903

Title: The role of corrective feedback in memory for contextual details

Authors: *A. S. HOWARD[1], L. E. BERNSTEIN[1], J. D. W. STEPHENS[2], A. A. OVERMAN[1]
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Abstract: Memory is typically better for information that is self-generated rather than passively read (Slamecka & Graf, 1978). When combined with feedback, incorrect generation can improve memory as well as correct generation (Metcalfe & Kornell, 2007; Kornell, Hays, & Bjork, 2009). Generation can have negative effects on memory for context features (e.g., Mulligan, 2004). Our recent research has shown that corrective feedback leads to better context memory than confirmatory feedback, and may contribute to enhanced recollection of the learning episode (Overman, Bernhardt, & Stephens, in prep). Neuroimaging research also suggests the hippocampus is involved in feedback learning (Dickerson & Delgado, 2015), which may account for better contextual memory with corrective feedback. Another possibility is that corrective feedback causes the learner to direct more attention to contextual details presented immediately

after the feedback. The objective of the present study was to test the extent to which the positive effect of corrective feedback on context memory depends on the timing of the contextual information relative to the feedback. We extended our prior work on generation, feedback, and context by modifying the timing of when participants received context information. Participants read or generated category exemplars, and typed them in blue or yellow font (contextual detail), with half of their generated responses randomly assigned as "correct" and given confirmatory feedback, and the other half assigned as incorrect and given corrective feedback (including the alternate exemplar that was the "correct" response). The effect of corrective feedback on context memory was reduced when the context preceded the feedback, suggesting that attention is an important factor in the effect of feedback on memory for contextual details.

Disclosures: A.S. Howard: None. **L.E. Bernstein:** None. **J.D.W. Stephens:** None. **A.A. Overman:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant R01MH080833 (EAK)

NSF-GRFP Fellowship DGE1258923 (SMK)

Sigma Xi Grants-in-Aid

Title: Valence-specific interactions between heart rate deceleration during encoding and subsequent memory vividness

Authors: *S. M. KARK, E. A. KENSINGER
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Abstract: Emotional memory studies have demonstrated greater activation in visual processing regions during encoding and retrieval of negative memories, compared to positive memories. Further, emotion work has shown that arousal-related heart rate deceleration responses are associated with enhanced visual perception and are correlated with activity in visual and affective processing regions. However, it is not known if heart rate deceleration responses during encoding of emotional stimuli influence later subjective memory strength in a valence-specific manner. The current functional magnetic resonance imaging (fMRI) study examined the effect of valence on the psycho-autonomic interaction (PAI) between the magnitude of heart rate deceleration during encoding and subsequent memory vividness. While undergoing concurrent fMRI and psychophysiological monitoring, participants studied 150 line-drawings of photos

followed by the complete colorful photo (50 negative, 50 positive, and 50 neutral). For each item, participants indicated whether they would "Approach" or "Back away" from the scene. After a 24-hour delay, participants were scanned while they completed a surprise recognition memory test. During test, participants were shown all of the previously studied line-drawings and an equal number of unstudied line-drawings. Participants made a button press to indicate if they thought the line-drawing was new (by pressing the 0 key) or—if they thought it was old—how vivid their memory was on a scale from 1-4. Parametric modulation analyses were conducted to examine the PAI effect between heart rate deceleration responses to the colorful photos during encoding and subsequent memory vividness ratings. Results revealed that, compared to positive and neutral memories, negative memories showed significant PAI effects in occipital and occipito-temporal regions (e.g., inferior occipital gyrus, lingual gyrus, fusiform gyrus) as well as the amygdala, beyond the separable main effects of heart rate changes and subsequent memory vividness. These results suggest that sensory and affective processing regions show valence-specific effects of arousal during encoding on the later subjective experience of memory during retrieval.

Disclosures: S.M. Kark: None. **E.A. Kensinger:** None.

Poster

169. Human Long-Term Memory: Encoding

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Program#/Poster#: 169.25/TT4

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R15AG052903

Title: fMRI activation likelihood estimation of item-item and item-context associative memory

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Abstract: Evidence exists that different subregions of the medial temporal lobe support different types of associations (e.g, item-item and item context; Diana, Yonelinas, & Ranganath, 2012). While there are many neuroimaging studies that examine associative memory (e.g., Ranganath, et al., 2004), and a few that directly compare item-item and item-context memory (e.g., Wong, et al., 2013), the methodological differences amongst the empirical studies and a focus on only a subset of the findings has limited broader conclusions regarding the neural mechanisms underlying associative memory. Thus, the objective of the present study was to conduct a quantitative meta-analysis of functional magnetic resonance imaging (fMRI) studies of item-item and item-context associative memory using a brain mapping computer program called GingerALE (www.brainmap.org). This meta-analysis uses an activation likelihood estimation to

compile a multitude of fMRI studies, which allows for identification of the foci that are consistently activated for item-item and item-context encoding, respectively. The studies that were included in the analysis were systematically collected using the following criteria: a full brain fMRI scan was conducted at encoding, encoding tasks examined either item-item or item-context declarative memory, and participants were healthy adults with no history of memory impairment or neurological damage. In order to collect the studies for the analysis the literature PubMed and PsycInfo databases were searched using the keywords “fMRI”, “associative memory”, “associative recognition”, “relational memory”, “item-item”, “item-context”, and “medial temporal lobe.” Results indicate differences in processing of different associations and help clarify the neural activity that supports successful associative memory.

Disclosures: **E.S. Deneen:** None. **A.A. Overman:** None.

Poster

169. Human Long-Term Memory: Encoding

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"Investissements d'Avenir" (ANR-11-IDEX-0007)

"BQR Accueil EC 16" of University Claude Bernard Lyon 1

Title: Fronto-parietal EEG inter-subjects synchronization during watching of naturalistic videos predicts subsequent memory recall

Authors: *V. B. BOGDANOV[1], C. BORDIER[2], V. MAZZA[3], E. MACALUSO[4]
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Abstract: Fronto-parietal ERPs during the encoding of simple stimuli can predict subsequent memory (Chen et al. 2014, *Exp Brain Res* 232:3175-90). However standard ERP methods do not allow extending these findings to more naturalistic conditions, such as memory for complex and dynamic stimuli. Inter-subject synchronization (ISS) provides us with a way to identify relevant brain responses associated with such stimuli (Hasson et al. 2004, *Science* 303:1634-40; Poulsen et al. 2017, *Sci Rep* 7:43916). Here, we recorded 64 channels EEG in 24 healthy volunteers while they watched short advertisement videos (8-10 sec) and hypothesized that ISS at fronto-parietal

sites would predict subsequent memory. In addition, we asked whether encoding either spatial or temporal details of the videos would modulate any subsequent memory effect. Each trial started with the instruction to encode either temporal or spatial details of the video (80 videos for each condition). This was followed by the video presentation, the memory test and a memory confidence question. The memory test comprised the presentation of a single frame extracted from the movie. On temporal trials the participants were asked whether the frame was extracted from the first or the second half of the video, while on spatial trials they had to judge whether the frame was in the same orientation as in the video or it was a mirror-reversed version. The ISS was calculated for each video, separately at each electrode. First, linear regressions between all possible pairs of participants were computed and the median of the regression-slopes was retained as the overall synchronization strength, irrespective of task and memory. This was highly significant at all electrodes ($p<0.001$), with peaks of significance over posterior sites. Next we recomputed the ISS values, now considering separately temporal vs. spatial trials and remembered (high confidence hits) vs. incorrect or low confidence trials. The corresponding 2x2 ANOVAs revealed a main effect of subsequent memory over fronto-parietal electrodes ($p<0.001$): that is, the EEG signal was more correlated between pairs of participants who confidently remembered a given video, compared to pairs of participants who failed to confidently recall the same video. The main effect of task and the task by memory interaction were not significant ($p>0.05$, for all electrodes). We conclude that inter-subject synchronization over fronto-parietal electrodes predicts subsequent memory for naturalistic stimuli, and that EEG-ISS enables studying high cognitive functions in contextually rich life-like conditions.

Disclosures: **V.B. Bogdanov:** None. **C. Bordier:** None. **V. Mazza:** None. **E. Macaluso:** None.

Poster

169. Human Long-Term Memory: Encoding

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Topic: H.02. Human Cognition and Behavior

Support: NSF BCS grant 1533511

CV Starr Foundation at Princeton University

Title: Competition between items during learning influences targeted memory reactivation during sleep

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Abstract: Prior work has demonstrated that, during wake, competition between memories can result in weakening of the competing memories (e.g., Lewis-Peacock & Norman, 2014). In two studies, we investigated the effects of memory competition during sleep on subsequent memory performance. Participants first learned arbitrary associations between specific environmental sounds and picture items (celebrities, landmarks, and common objects). Some sounds were linked with one item (singular), whereas some were linked with two items from separate categories (paired). Next, participants learned the spatial location of each item against a background grid, where each paired item was assigned either a high or low monetary reward to be given at pre- and post-nap tests. Critically, we manipulated the level of competition between paired items for different groups of participants by either presenting them consecutively or interleaved (direct or indirect competition, respectively). Next, participants took a pre-nap test and slept in the lab. During intervals of slow-wave sleep, we presented all singular and half of the paired sounds. After the nap, participants took a final memory test. The level of competition strongly impacted the effect of cueing during sleep. Under indirect competition, cueing improved retention for both high and low reward paired items relative to uncued items. Analyzing paired items showed that cueing improved one of the two items, but not both. Under direct competition, we found no overall cueing effect; however, when both items of a pair were well-learned prior to the nap (i.e. when competition was strongest), cueing impaired memory. To find measures of reactivation, we focused on oscillatory power in the post-cue period for the theta (5-8 Hz) and sleep spindle bands (11-16 Hz), which we have previously found to predict subsequent memory. First, we analyzed differences between singular and paired items. In both conditions, paired sounds showed higher spindle power than singular sounds between 300-700 ms, whereas the opposite was true between 1000-1500 ms. Spindle power at 700-1200 ms predicted better memory for the singular sounds. To probe the role of competition, we next focused on paired sounds for which both items were well-learned prior to the nap. In both competition conditions, spindle power between 1200-1500 ms predicted better retention; in contrast, theta power between 1200-2200 ms predicted better retention in the indirect condition but worse retention in the direct condition. Together, these results suggest sleep reactivation under low competition strengthens memory but under high competition weakens it.

Disclosures: **J.W. Antony:** None. **L. Cheng:** None. **P.A. Pacheco:** None. **B. Wang:** None. **K.A. Paller:** None. **K.A. Norman:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.28/TT7

Topic: H.02. Human Cognition and Behavior

Title: Glucose effect on event model memory

Authors: *M. TOMBLIN[1], G. RADVANSKY[2], M. ROY[1], C. FOX, 46556[1]
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Abstract: Some studies have shown that glucose facilitates memory, particularly under conditions of challenged cognitive resources, as with older adults or when doing tasks that require high cognitive load. However, other studies have failed to show this glucose-facilitating effect. This inconsistency might be due to methodological differences such as the timing of glucose administration or the delay in memory testing. To solve this dilemma, we designed a study that investigated the effect of glucose administration on memory at different times during memory processing. Thirty-seven college students, that fasted for eight hours prior to testing, read four historical accounts and were tested on Surface Form (verbatim memory), Textbase (ideas in the text) and Event Model (representation of the described situation) memory few minutes after encoding and 7 days later. Participants ingested a glucose drink prior to encoding (Group A), following encoding (Group B) or prior to a 7-day delayed retrieval (Group C). Saccharin was given as a placebo in all three groups. On both testing days, blood glucose level was measured at fasting and following memory testing. To date, statistical analyses show that a 7 day delay resulted only in a decrease in Textbase memory. Glucose did not enhance memory in any of the groups. However, fasting blood glucose level has an effect on Event Model memory that depends on the time of memory testing. People with relatively high fasting blood glucose levels perform lower than those with low fasting blood glucose levels when tested on memory soon after encoding, however that effect is reversed after 7 days later. Relatively high fasting blood glucose level on Day 7 also resulted in enhanced Surface Form or verbatim memory that was specific for people who ingested glucose that same day. In conclusion, fasting blood glucose level rather than glucose administration may affect memory. More testing will be done to clarify these findings.

Disclosures: **M. Tomblin:** None. **G. Radvansky:** None. **M. Roy:** None. **C. Fox:** None.

Poster

169. Human Long-Term Memory: Encoding

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 169.29/TT8

Topic: H.02. Human Cognition and Behavior

Title: Survival of the self: Neural examinations of survival encoding

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Abstract: The survival encoding effect, or “Adaptive Memory” shows a memory advantage to information processed in the context of one’s own survival. The self-reference effect also shows a memory advantage to information processed in reference to the self. Survival encoding gives an advantage to memory recall to a greater degree than self-reference. We examined how each of these effects are supported by the brain, and whether the survival encoding effect operates functionally as a distinct encoding process or as an augmented form of self-reference.
Survival encoding and self-referential paradigms were adapted to examine the same noun words, parsing out self and other for each encoding process. A within-subjects design was used to effectively compare fMRI response across 6 encoding conditions: Survival Self, Survival Other, Self-Reference, Other-Reference, Pleasantness (a deep encoding comparison) and Upper Case/Lower Case (a shallow encoding comparison). Participants (n =25) encoded 30 words per condition over 5 runs while functional MRI data were collected using a 3T scanner. Following the scanning session, participants completed a surprise free recall task.
Behavioral results on the free recall task were consistent with previous findings, demonstrating a memory advantage to self-reference and a further memory advantage to stimuli processed using survival encoding. Patterns of neural activation differed significantly between survival and reference conditions. Self-referential encoding recruited cortical midline structures including the medial prefrontal cortex more than survival encoding, indicating these encoding strategies are distinct and that survival encoding is more than merely an enhanced self-reference effect. Compared to self-reference, survival encoding was associated with increased activation in the left inferior parietal lobule, left middle temporal gyrus, and left & right middle frontal gyri. Additionally, survival encoding effect abolishes the self-other cortical midline recruitment associated with self-reference, consistent with its dominance in memory formation. Further, contrasts comparing self-reference and survival encoding to the Pleasantness condition confirm that adaptive memory encoding processes cannot sufficiently be described by classical deep processing effects.
Processing neutral information in regard to one’s own survival provides a unique memory advantage and cannot be understood by the same medial prefrontal areas known to drive the self-reference effect. These results provide evidence that “Adaptive Memory” is a distinct effect with a unique neural process at encoding.

Disclosures: **T. Eaton:** None. **A.K. Anderson:** None.

Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 170.01/TT9

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) program (cooperative agreement N66001-14-2-4032).

Title: Pathological ripple oscillations disrupt memory encoding during a free recall task

Authors: Z. WALDMAN[1], B. M. BERRY[4], M. T. KUCEWICZ[5], B. ELAHIAN[1], J. STEIN[6], S. DAS[7], R. GORNIAK[2], A. SHARAN[2], R. E. GROSS[10], C. S. INMAN[11], B. C. LEGA[12], K. A. ZAGHLOUL[13], B. C. JOBST[14], K. DAVIS[8], P. WANDA[9], M. KHADJEVAND[5], D. S. RIZZUTO[7], M. J. KAHANA[9], G. WORRELL[5], M. SPERLING[3], *S. A. WEISS[2]
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Abstract: Objective: High-frequency neurophysiological activity (HFA, >30 Hz) mediates memory encoding across brain networks. However, brief (~30-60 msec) high-frequency oscillations (HFO) in the ripple band (80-200 Hz) are generated in epileptogenic brain regions and may disrupt memory networks. We examined whether ripple events detected from intracranial EEG (iEEG) recordings during word presentation correlated with failed word recall.
Methods: We applied a validated wavelet topographical algorithm to detect and quantify ripple events in depth iEEG recordings from 7,630 unique locations, during 58,312 word presentation trials, in 117 DARPA RAM patients. We used naïve Bayesian (NB) machine learning to quantify the relationship between ripple event occurrence during each encoding trial, and the behavioral recall of the word following a distractor period.
Results: In contrast to the HFA that mediate memory encoding, ripple events occurred very infrequently. The probability of ripple on epileptiform spike (RonS) events was increased in the seizure onset zone (SOZ) [true RonS: 0.3%, false RonS: 0.17%], compared to the non-SOZ [true Rons: 0.09%, false RonS:0.04% $p<0.05$,$p=0.08$]. The probability of ripple on oscillation (RonO) events trended higher in the irritative zone, as compared to healthy brain regions (0.034% vs. 0.015%, $p=0.11$). We constructed and cross-validated a NB model revealing a 26.85% loss. Using the model, we found that ripple events correlated with failed encoding. RonO events were more predictive of failed encoding, compared with RonS events. Ripple events most often occurred in temporal and limbic regions, and disrupted encoding (72.37% baseline failed recall probability vs. 81.42-99.88%, Table 1). In other regions ripple events increased the probability of encoding failure, but not in left limbic or parietal regions.
Significance: Pathological high-frequency oscillations in the ripple band generated during word presentation correlate with failed recall. Ripples that occur in the absence of epileptiform spikes are even more likely to disrupt memory encoding.

Table-1
Probability of Failed Encoding %(# events)

	TRonS	FRonS	RonO
'Left Cerebrum'	75.62%(1661)	88.54%(2232)	97.28%(140)
'Right Cerebrum'	75.13%(681)	86.96%(1913)	96.14%(83)
Both	80.19%	95.70%	99.74%
None	**69.84%**		
'L-Frontal Lobe'	54.29%(927)	91.78%(145)	99.88%(6)
'L-Limbic Lobe'	**74.34%(771)**	**72.99%(1524)**	**70.69%(41)**
'L-Occipital Lobe'	84.18%(15)	100.00%(147)	100.00%(9)
'L-Parietal Lobe'	72.48%(117)	63.38%(133)	54.27%(13)
'L-Sub-lobar'	59.41%(58)	85.12%(277)	99.50%(5)
'L-Temp Lobe'	**83.38%(452)**	**96.00%(1643)**	**99.69%(124)**
'R-Frontal Lobe'	92.10%(135)	99.86%(434)	100.00%(5)
'R-Limbic Lobe'	**81.42%(513)**	**93.44%(1275)**	**98.03%(72)**
'R-Occipital Lobe'	100.00%(1)	100.00%(15)	100.00%(0)
'R-Parietal Lobe'	99.99%(139)	100.00%(77)	100.00%(1)
'R-Sub-lobar'	87.71%(21)	98.98%(214)	99.99%(2)
'R-Temporal Lobe'	**84.80%(187)**	**97.32%(698)**	**99.88%(86)**
None	**74.81%**		

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 170.02/TT10

Topic: H.02. Human Cognition and Behavior

Support: DARPA N66001-14-2-4032

Title: Spatiotemporal dynamics of gamma frequency oscillations reveal a widespread network for human memory processing

Authors: *M. T. KUCEWICZ[1], B. M. BERRY[2], L. R. MILLER[3], F. KHADJEVAND[4], P. WANDA[5], J. M. STEIN[7], M. R. SPERLING[8], R. GORNIAK[8], K. A. DAVIS[7], B. C. JOBST[9], R. E. GROSS[10], B. C. LEGA[11], S. A. SHETH[12], M. S. STEAD[3], D. S. RIZZUTO[5], M. J. KAHANA[6], G. A. WORRELL[3]
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Abstract: Human memory is supported by coordinated activity in a network of specific cortical and subcortical brain regions. In particular, oscillations recorded in the gamma frequency range (30-150 Hz) of the local field potential have been proposed to reflect synchronous firing of neuronal assemblies but their role in memory or the associated sensory and attentional processes remains elusive. To investigate the role of gamma oscillations in human cognition we used intracranial recordings from electrodes implanted on the cortical surface and penetrating into the mesial temporal lobe in a large set of epilepsy patients (N=186) performing free recall verbal memory tasks. Patients memorized lists of words presented on a laptop computer screen for subsequent recall, which followed a short distractor task. Individual bursts of increased gamma frequency power were detected in the local field potential signal during the stimulus presentation epochs (Kucewicz et al. 2014, Brain 137(8) & Kucewicz et al. 2017, Brain 140(5)). The gamma bursts were quantified in 50 ms time bins across 26 anatomically distinct cortical gyri, the hippocampus and the amygdala, to compare the rates on trials with subsequently remembered and forgotten words. We found significant differences in the rates of gamma bursts between the remembered and forgotten condition, which we defined as the subsequent memory effect (SME), across the entire network of brain regions activated in the tasks. SME followed a sequence of the visual information processing stream appearing first in the sensory areas of the occipital lobe and late in the higher order associational areas of the frontal lobe. In all of those regions, we report a characteristic ‘flip-over’ pattern in SME directionality switching at time of the peak induced gamma response from negative, i.e. less gamma bursts on the remembered words trials, to positive, i.e. more gamma bursts on the remembered trials, and then back to negative towards the end of the word presentation epoch. Our results elucidate the role and organization of gamma oscillations in memory processing, which suggest a wide-spread network of early sensory and higher order executive brain areas in successful memory encoding. In conclusion, gamma oscillations are proposed to guide novel mapping and stimulation technologies in specific anatomical space and time of human memory processing.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 170.03/TT11

Topic: H.02. Human Cognition and Behavior

Support: DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)

Title: Changes in low frequency activity depend on location of electrical stimulation in the human cortex

Authors: *U. R. MOHAN[1], A. WATROUS[1], M. SPERLING[3], A. SHARAN[4], G. WORRELL[6], B. BARRY[6], B. C. LEGA[7], B. C. JOBST[8], K. DAVIS[9], R. E. GROSS[11], S. A. SHETH[2], S. DAS[12], J. STEIN[10], R. GORNIAK[5], D. S. RIZZUTO[13], M. J. KAHANA[14], J. JACOBS[1]
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Abstract: Brain stimulation shows enormous clinical potential as a treatment for a variety of neurological conditions; however, studies using deep brain stimulation to enhance memory have not yielded consistent results. Similarly, early human brain stimulation literature has had mixed theories on the excitatory and inhibitory effects of stimulation on local and connected regions. We investigated the effects of direct electrical stimulation on the human brain to understand how changes in stimulation location, amplitude, frequency, and duration induce changes in activity across the brain. We collected human electrocorticographic recordings from neurosurgical patients while stimulation was systematically delivered for different combinations of stimulation location, amplitude, frequency, and duration. We measured low frequency activity prior to the delivery of stimulation and following stimulation. Mapping changes in low frequency activity across the brain showed a diversity of patterns both within and between subjects. Increasing frequency and amplitude resulted in more widespread significant changes in low frequency activity. However, changes in stimulation location resulted in the most distinct pattern changes in low frequency activity between stimulation locations. These results suggest that selecting a location for electrical stimulation is more critical than selecting a stimulation frequency at a given location to yield desired changes to low frequency activity when modulating behavior and cognition.

Disclosures: **U.R. Mohan:** None. **A. Watrous:** None. **M. sperling:** None. **A. Sharan:** None. **G. Worrell:** None. **B. Barry:** None. **B.C. Lega:** None. **B.C. Jobst:** None. **K. Davis:** None. **R.E. Gross:** None. **S.A. Sheth:** None. **S. Das:** None. **J. Stein:** None. **R. Gorniak:** None. **D.S. Rizzuto:** None. **M.J. Kahana:** None. **J. Jacobs:** None.

Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: Advanced T32 Training Grant in Neurobiology and Behavior

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DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)

Title: Identifying single-unit activity in the human medial temporal lobe relating to associative spatial memory

Authors: *M. TSITSIKLIS[1], A. WATROUS[2], S. QASIM[2], J. MILLER[2], S. A. SHETH[3], C. SCHEVON[3], R. E. GROSS[5], C. S. INMAN[6], M. SPERLING[7], J. STEIN[9], S. DAS[10], R. GORNIAK[8], D. S. RIZZUTO[11], M. J. KAHANA[11], D. SHOHAMY[4], J. JACOBS[2]
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Abstract: The hippocampus and surrounding medial temporal lobe (MTL) cortices are essential for the encoding of spatial memory. Phase locking of MTL neurons to ongoing oscillations has been shown to predict subsequent memory for images in humans and to play a role in associative memory processing in rodents. However, how single-neuron activity is coordinated to support spatial memory remains relatively unknown. We recorded single-unit data from intractable epilepsy patients while they played Treasure Hunt, a video-game-like task that measures people's ability to remember links between objects and locations. In each trial, patients explored a virtual beach to reach treasure chests that revealed hidden objects, with the goal of encoding the location of each encountered item. In a subsequent retrieval phase patients were asked to identify the location in which each object was originally presented. Our data analyses focused on

understanding how neuronal firing and oscillations relate to spatial memory. During the encoding of object-place associations there was an increase in firing rate in a number of cases, although firing rate itself was not predictive of subsequent memory. There was also an increase in activity in the theta band during object presentation. The activity of many MTL neurons was phase locked to theta during encoding, as well as to other low frequency oscillations. We examined how differences in the presence of phase locking and the preferred phase to subsequent recall performance. In approximately 10% of the neurons, we found that differences in either the presence of phase locking or the preferred phase during encoding predicted successful or unsuccessful recall. This differential timing of spikes relative to low frequency oscillations in the local field potential provides evidence for a distinct processing state during the encoding of successful spatial memory in the human MTL.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Program#/Poster#: 170.05/TT13

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH55687

DARPA N66001-14-2-4032

T32 NRSA 3T32NS091006-02S1

Title: The connectivity "tilt": A detailed map of low-frequency neural synchronization and high-frequency desynchronization within human MTL during learning

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Abstract: Storing episodic memory is an inherently integrative process, long conceptualized as a process that binds information about new experiences to a prevailing neural context. Neural synchronization, or the correlated spectral activity between different parts of the brain, has been proposed as a general mechanism for this binding process. However, the dynamics of neural synchronization in the human brain are largely unexplored, especially at the fine spatial scales of critical memory areas like the medial temporal lobe (MTL). Here, we characterize the neural synchronization within substructures of human MTL that occurs during memory encoding and retrieval. We leverage a large dataset of 61 subjects fitted with indwelling electrodes in the MTL and use connectivity measures which are resistant to artifacts of volume-conduction. We find that, during successful encoding, MTL substructures tend to synchronize with each other at low frequencies (3-4Hz), with parahippocampal cortex and dentate gyrus emerging as hubs of synchronous activity (Figure 1). At higher frequencies (gamma, 30-105Hz), we observe strong desynchronizations of neural activity but note that synchronization is observed if volume-conduction artifacts are not considered, refuting longstanding notions of intra-MTL gamma synchronization. Taken together, these results suggest that memory encoding processes in the MTL reflect the same dynamics as found at larger anatomic scales – increases in connectivity are observed at low frequencies, while asynchronous increases in local spectral power are observed at high frequencies. Consequently, future efforts to tease apart the mechanisms of learning and memory in the MTL should be cautious when claiming evidence of high-frequency synchronization, or invoking the necessity of high-frequency connectivity in hippocampal and MTL function.

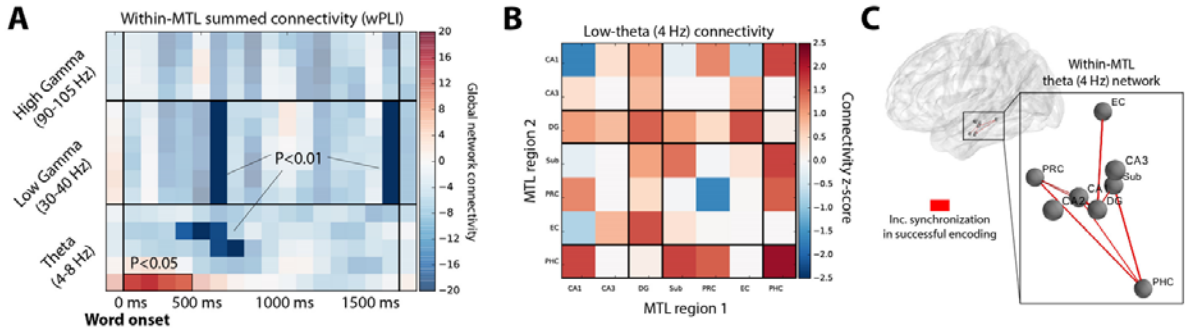

Figure 1. A: Summed within-MTL weighted phase-lag index connectivity (wPLI) reveals desynchronizations (blue) in gamma correlating with successful encoding, and an early synchronization (red) at 4 Hz. **B:** Adjacency matrix representing connection between MTL substructures during the significant 4 Hz theta period from A. Dentate gyrus (DG) and parahippocampus (PHC) have statistical hub properties ($P<0.05$). **C:** Anatomic visualization of network in B, thresholded for clarity.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: This work was supported by the DARPA Restoring Active Memory (RAM) program (Cooperative Agreement N66001-14-2-4032)

Title: Evaluating the effects of targeted electrical stimulation on interictal spiking across stimulation sites and parameters

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Abstract: Interictal spikes are transient electrographic events linked with impaired cognition in epileptic patients. Rates of interictal spiking correlated negatively with behavioral performance in a delayed free recall memory task during both encoding and recall periods in several brain regions (Horak et al., *Epilepsia*, 2017). Moreover, studies of deep brain stimulation (DBS) report reductions in interictal spiking following chronic stimulation. However, the influence of stimulation site, amplitude, and frequency during direct electrical stimulation of the human brain has yet to be systematically examined in the context of interictal spiking. We investigated the influence of these factors across 97 stimulated sessions (n = 72 open-loop, n = 25 closed-loop) of the delayed free recall task collected for the Restoring Active Memory (RAM) project. Neurosurgical patients were implanted with subdural and/or depth electrodes for a period of electrocorticographic (ECoG) clinical monitoring. For each task session, a single bipolar electrode pair was stimulated during a subset of word presentations, most often in medial (n = 43), superolateral (n = 22), and inferior (n = 14) temporal lobe structures. Stimulation frequencies were 10, 25, 50, 100, and 200 Hz and stimulation amplitude ranged between 250 and 3,500 μA. Spike rates were compared across matched pairs of stimulated and unstimulated

segments from sessions using the Wilcoxon signed-rank test and between parameter groups using the Mann-Whitney U-test. Our findings indicate that a closed-loop stimulation paradigm more consistently suppresses interictal spiking than does an open-loop approach and that the modulatory effect of electrical stimulation varies significantly across the sites and parameters of stimulation.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 170.07/TT15

Topic: H.02. Human Cognition and Behavior

Support: NIH HL105355

Title: Novel system for physiologic closed-loop restoration of breathing using cranial nerve derived inputs and electrical stimulation

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Abstract: *Introduction:* For 40 years, pacing devices have been considered to treat patients with neurogenic apnea (Glenn, 1972). The promise of this class of devices has been seen in its contrast to positive-pressure ventilation (PPV) and Mechanical Ventilation (MV), the gold standard of the time for patients with SCI and other critical afflictions. A phrenic pacing device allows the patient to breathe without intubation and the associated discomfort and cost. We propose a novel, physiologically closed-loop that improves upon current technology and alleviates concerns associated with MV. *Method:* A device and method is provided for electrically stimulating the diaphragm to control breathing in a novel physiologic manner. The Input for the device is the patient's own physiologically determined time and depth of breathing based on cranial nerve innervated upper airway structures. Spectral decomposition of these peripheral signals is handled within the device in real time and is shown to result in robust breathing restoration even at times of low signal-to-noise. Finally the Output of the device is electrical stimulation for the main muscle of breathing, the diaphragm. Testing was conducted in n=4 rodent models with spinal cord blunt injury. Dual record-stimulating electrodes were

implanted bilaterally on the diaphragm (Alvarez-Argote 2015) and recordings were taken during eupnea and dyspnea conditions with the device and method in place while stimulation was delivered based on above-lesion inputs. EMG probes for closed-loop procedures were implanted in laryngeal structures, innervated above the lesion, providing the necessary inputs for the pacing to be achieved.*Results*: Accuracy of >90% was achieved for timed stimulation according to the above-lesion inputs was achieved in all three subjects and pCO2 taken at interval showed no deviation BNL across a 10 minute testing period. However in one subject, testing was not conducted due to extensive mid-cervical damage during the spinal injury procedure. Whole body plethysmography and diaphragm EMG were measured POD 3. There were no significant changes in breathing parameters during eupnea or exposure to hypoxia (10% O2) - hypercapnia (5% CO2) with utilization of the pacing system.*Conclusions*: This platform illustrates a method to provide ventilation in cases of severe dyspnea resulting from SCI. For spinal cord injury (SCI), this includes those above the C3 level. The phrenic nerve must remain intact and therefore its motor nucleus must remain after any injury or illness. In many cases of SCI, there is mid-cervical damage which potentially damages the phrenic motor nucleus, leaving no viable target to electrically pace.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: DARPA RAM N66001-14-2-4032

Title: Direct brain stimulation in closed-loop to modulate human episodic memory encoding

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Abstract: Episodic memory encoding fluctuates in its efficiency from moment to moment, leading to variability in the ability to store information for later retrieval. Oscillatory brain

activity both during and prior to an event predicts later memory, suggesting that direct manipulation of brain activity through stimulation could be used to modulate memory function. Past studies that have applied electrical stimulation in humans via intracranially implanted electrodes have shown mixed results, with some suggesting memory enhancement but many showing memory disruption. In prior work using an open-loop approach, we found that stimulation's effect on memory encoding was dependent on the brain's encoding state prior to stimulation delivery. Stimulation applied during poor encoding states increased memory performance, suggesting that stimulation might consistently increase memory function if timed to coincide with poor memory states. Here, we present a direct test of this hypothesis using a closed-loop design. Epileptic patients with intracranially implanted electrodes performed a free recall task in which we decoded the brain's encoding state for each word. We used a subject-specific multivariate classifier trained on previous record-only electroencephalographic data to decode probability of memory success for each item, and triggered stimulation if the classifier indicated that later recall was unlikely. Across the group, stimulation increased memory performance relative to a matched non-stimulated condition, with several instances of reliable within-subject improvement. Classifier generalization to the closed-loop session predicted stimulation's effect on memory, highlighting the importance of successful targeting of poor memory states. Stimulation applied to lateral temporal cortex outperformed stimulation to other areas, including medial temporal lobe, suggesting that superficial areas can be targeted to modulate memory. The data identify conditions under which stimulation can be used to improve memory, and suggest applications to treating memory dysfunction.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: DARPA Grant N66001-14-2-4032

Title: Design of a flexible sense and stimulation system to investigate memory restoration

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Abstract: Memory impairment affects millions of people worldwide and treatment options for these patients are limited. A potential method to treat this is electrical stimulation of the brain. Current efforts have been focused on generating a large dataset of intracranial recordings and stimulation in epilepsy patients (DARPA 'Restore Active Memory' (RAM) project) to quantify memory performance with a significant number of subjects.
The goal of the RAM project is to develop a system for clinical use. To address this goal, a staged approach has been taken: 1) demonstrate memory improvement with available research systems, 2) develop an external system with implantable grade components for fast prototyping of algorithms, 3) demonstrate memory improvement with external system, 4) refine system design for development of a memory prosthesis. This abstract describes the outcome of step 2. A AA-battery powered external neural stimulator was designed incorporating next generation implantable grade integrated circuits that are compatible with existing electrodes and clinical methodology. Critical inputs for the system were defined and a system was designed, verified, and validated.
The system is capable of monitoring 256 electrodes simultaneously at a rate of up to 1000 Hz and streaming the data in real time via either USB or WiFi to the host computer where all channels can be displayed and every channel is stored. A 1ms timer count is included with sense data for system synchronization. Each sense channel has a noise floor less than 300nV/root(Hz) and can be filtered to limit high frequency intrusions. System stimulation can be applied on up to 128 pairs of anodes and cathodes with a stimulation range of 4uA to 12.5mA. Pulse width, frequency, pulse sets, and amplitude are adjustable via the software programming interface and can be programmatically adjusted to any value below the charge density limit. Round trip system latencies are less than 25ms from the time an event of interest is measured to the time an adjusted stimulation pulse is administered. The collected data can be analyzed offline to determine classification of good and bad memory conditions and stimulation electrodes and control methodology can be defined in a file. This file can be used for a custom sense, stimulation, and control policy settings for each patient given their unique brain mapping.
Initial system deployment focused on replicating existing clinical findings. The next steps for use of the system will be increased programmatic interfacing with the system for truly adaptive stimulation based on real time assessment of patient brain state and further refinement of the design of a memory prosthesis.

Disclosures: **H. Orser:** A. Employment/Salary (full or part-time):; Medtronic, Inc. **G. Loxtercamp:** A. Employment/Salary (full or part-time):; Medtronic, Inc. **D. Carlson:** A. Employment/Salary (full or part-time):; Medtronic, Inc. **M. Swat:** None. **M. DePalatis:** None. **M.J. Kahana:** None. **T. Denison:** A. Employment/Salary (full or part-time):; Medtronic, Inc. **D. Rizzuto:** None.

Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Program#/Poster#: 170.10/TT18

Topic: H.02. Human Cognition and Behavior

Title: Frequency and phase-tuned neuronal firing supports goal-directed human navigation

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Abstract: Prior human studies have identified 1) spatially-tuned neuronal firing during navigation and 2) neuronal phase locking to local field potential oscillations, yet whether these phenomena relate to one another remains unanswered. We hypothesized that the phase and frequency of slow oscillations would encode information about navigational goals and spatial locations in addition to firing rate changes. To understand the tripartite relation between navigation, cellular responses, and oscillations, we analyzed 482 single-neurons and LFP signals from the hippocampus, entorhinal cortex, and parahippocampal gyrus of 12 epilepsy patients performing a virtual taxi-driver task. We developed a novel algorithm to identify the instantaneous phase and frequency of narrowband oscillations exceeding the background spectrum and then used either firing rate or the instantaneous phase and/or frequency of the narrowband LFP during neural spiking to predict navigational variables. We observed significant classification of goal and location information using firing rate in 87 (18%) and 49 (10%) of neurons respectively, each of which exceeded chance levels (binomial test, $p<.00001$) and were confirmed using a bootstrapping procedure. In the remaining 395 neurons in which firing rate changes did not predict the navigational goal, significant decoding was possible using either the phase or frequency of low-frequency oscillations during neural firing in 28 (7%) and 61 (15%) of neurons, respectively. Each of these proportions were significantly above chance and similar results were obtained when decoding spatial locations in the environment. We conclude that spiking relative to slow oscillatory phase and frequency conveys additional navigational information beyond firing rate changes in the human medial temporal lobe.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: NSF Graduate Research Fellowship

NIH 1-R01-MH 104606-02

Title: Human place cell activity and remapping during a virtual spatial memory task

Authors: *S. E. QASIM[1], A. SHARAN[4], C. WU[4], M. SPERLING[5], S. SHETH[2], G. MCKHANN[2], C. SCHEVON[3], E. SMITH[2], B. LEGA[6], J.-J. LIN[6], R. E. GROSS[7], J. T. WILLIE[7], C. S. INMAN[7], J. MILLER[1], J. JACOBS[1]
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Abstract: Many of the same brain areas involved in spatial representation have been found to play a role in the encoding and recall of memory. Remapping of medial temporal lobe (MTL) activity has been proposed as a candidate mechanism for the storage of distinct representations necessary for this flexibility. In order to test this theory, we analyzed single-neuron data recorded from the hippocampus, entorhinal cortex, amygdala and cingulate cortex of neurosurgical patients with epilepsy performing a virtual-reality spatial memory task. This task encouraged the subjects to pay sustained attention to their location by moving them along a linear track at varying speeds. In encoding trials an object would appear on the track and patients would press a button when they reached the object's location. In recall trials the object would not be visible and patients would press a button when they reached the remembered location of the object. Because the subjects' speed is changed randomly, it requires that they carefully attend to their location throughout movement.Of the more than 315 single units recorded during this task, approximately 25% were significantly modulated by the subject's perceived location, the object's perceived location, or an interaction between them. Inspection of this population of cells revealed several patterns of activity, primarily consisting of stable, static place cells (~30%), place cells that remapped to different preferred locations dependent upon the perceived location of the object (~50%), and cells modulated by object location alone (~20%). These cells were not modulated by the subjects' response nor did they show a clear relationship to movement speed. Place modulated cells in the entorhinal cortex also showed a consistent pattern of theta modulation indicating potential grid-like activity on the linear track. Work is ongoing to characterize these cells and their relation to spatial memory.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Program#/Poster#: 170.12/TT20

Topic: H.02. Human Cognition and Behavior

Title: Hippocampal-parietal interactions during retrieval of true versus false memories

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Abstract: fMRI evidence has implicated the lateral and mesial parietal lobe in memory retrieval, especially the mesial parietal structures such as the precuneus and lateral locations such as the angular gyrus. Previously, gamma band oscillatory power in the temporal cortex and hippocampus was shown to differentiate correct retrieval events from those in which events with incorrect contextual information were retrieved. However, older studies included few electrodes from the lateral and mesial parietal areas that are highly involved in retrieval, and to date no examination of hippocampal connectivity has been included during the analysis of true versus false episodic memories. We analyzed oscillatory activity from 24 patients who underwent stereo EEG electrode implantation for seizure localization. All of these patients had electrodes inserted into the anterior and posterior hippocampus along with the precuneus, posterior cingulate, angular/supramarginal gyrus, parahippocampus, and lateral temporal cortex (these regions were common to all subjects). We demonstrate an increase in hippocampal gamma activity during correct recall in agreement with previously published findings that does not differ among anterior or posterior hippocampal electrodes. Lateral parietal locations demonstrate the most robust gamma band power changes during correct versus incorrect retrieval events, indicating this region may be implicated in the encoding of temporal contextual information. Hippocampal-mesial parietal connectivity, especially with the precuneus, was strongest in the theta range during correct retrievals. Overall, our results shed new light on brain regions critical for item retrieval, especially for temporal contextual information. We place our findings within the existing human fMRI and iEEG literature, specifically how our data may fit with theories of postero-medial versus antero-temporal complementary memory systems governing human memory-related behavior.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: DARPA RAM

Title: Patterns of directed connectivity during episodic memory encoding and retrieval

Authors: ***J. W. GERMI**[1], V. S. NATU[2], J. STEIN[3], D. S. RIZZUTO[4], M. J. KAHANA[5], B. C. LEGA[6]
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Abstract: Animal and human electrophysiological data have provided evidence for connectivity changes in the hippocampus that occur during the encoding and retrieval of episodic memories. Greater hippocampal connectivity with widespread cortical regions including the parahippocampus, prefrontal cortex, and parietal structures such as the precuneus has been observed. In rodents, item encoding and retrieval is associated with differential directional connectivity between the hippocampus and prefrontal cortex during periods of the time series. These data build upon rodent studies showing that entorhinal-hippocampal connectivity also shows evidence of differential information flow during different phases of mnemonic processing. However, in humans, directional connectivity differences have not been reported. We present data from 54 human subjects who performed a verbal free recall task. Applying granger causality, mutual information and lagged coherence to iEEG signals during an episodic memory task, we investigate the directional relationship between the anterior/posterior hippocampus and other regions of the brain known to be involved in memory processes including the entorhinal cortex, lateral temporal cortex and mesial parietal lobe. We compare these directed relationships during both an encoding and a retrieval period. Briefly, we observe strong directional differences between the posterior hippocampus and lateral parietal structures including the angular gyrus strongest at 9 Hz during item retrieval. In temporal lobe regions, these effects were stronger during encoding. We place our findings in the context of existing theories of retrieval--related activation in this area and a possible role in resting state networks.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: DARPA Cooperative Agreement N66001-14-2-4032

NIH grant MH55687

Title: Intrinsic functional architecture of cortico-hippocampal networks determines episodic memory formation in humans

Authors: *J. E. KRAGEL[1], T. D. PHAN[1], P. A. WANDA[1], J. M. STEIN[2], S. DAS[3], R. GORNIAK[4], M. R. SPERLING[5], A. D. SHARAN[5], C. S. INMAN[6], B. C. LEGA[7], K. A. DAVIS[3], G. A. WORRELL[8], M. T. KUCEWICZ[8], B. C. JOBST[9], K. A. ZAGHLOUL[10], S. A. SHETH[11], D. S. RIZZUTO[1], M. J. KAHANA[1]
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Abstract: The human brain contains cortico-hippocampal networks that exhibit increased activity during successful memory formation. It has not been directly tested whether endogenous fluctuations in the recruitment of these networks account for variability of human memory function. We recorded neural activity from epilepsy patients during a free-recall task and during task-free periods. We identified consistent hippocampal networks from correlated fluctuations of band-limited signal in both theta (3-4 Hz) and gamma (> 70 Hz) bands, independent of cognitive state. We show that intrinsic dynamics within these hippocampal networks predict encoding-related activity within the hippocampus during successful memory formation. These findings help to resolve the variability puzzle by showing how endogenous activity across distributed cortical networks primes the hippocampal system to successfully form new memories.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: Cooperative Agreement N66001-14-2-4032

Title: Neural signatures of location and movement in a human spatial memory task

Authors: *J. MILLER[1], A. WATROUS[1], S. LEE[1], M. SPERLING[3], A. SHARAN[3], G. WORRELL[4], B. BERRY[4], B. C. LEGA[5], B. C. JOBST[6], K. DAVIS[7], R. E. GROSS[8], S. A. SHETH[2], S. DAS[9], J. STEIN[7], R. GORNIAK[3], R. GORNIAK[3], R. GORNIAK[3], D. S. RIZZUTO[10], J. JACOBS[1]
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Abstract: Studies of the electrophysiological correlates of successful memory encoding in humans have been largely confined to the domain of item learning in the absence of a salient spatial context, where successful encoding is often linked to increases in high frequency oscillatory power and decreases at low frequencies. In order to investigate the neural signals associated with the formation of memories for item locations, we created a novel 3D spatial paired-associates task called Treasure Hunt. We recorded intracranial electrocorticographic activity from neurosurgical patients as they explored a virtual beach and learned the locations of hidden objects. We subsequently tested location memory by asking patients to recall where specific objects were encountered. In contrast to many studies of item memory, successful item-location memory was accompanied by a general increase in low frequency oscillatory power, and this effect was most prominent in the anterior temporal lobe at frequencies below 10 Hz as well as in the left hippocampus at frequencies below 4 Hz. We also found that periods of virtual movement in the task elicited significantly greater 1-4-Hz activity compared to periods of stillness in the right hippocampus. These results highlight the dual role of the hippocampus in spatial memory and navigational function and suggest a lateralization of these processes. In addition, we were able to predict item-level performance at above chance levels using a logistic regression classifier. The accuracy of the classifier improved as we increased the number of included electrodes, providing evidence that memory for spatial locations is not simply a univariate signal isolated to precise anatomical locations.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Topic: H.02. Human Cognition and Behavior

Support: NIH

Title: Machine learning based classifier to predict episodic memory recall performance in epileptogenetic patients

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Abstract: Machine learning classifiers have been employed to predict encoding success based upon ongoing oscillatory information in human intracranial EEG. Such an approach has been used to guide the timing of responsive stimulation administration with the goal of influencing encoding success. We sought to build upon these existing methods and use machine learning to test the relative contributions of oscillatory information from the hippocampus and several temporo - parietal locations including the angular gyrus, precuneus, posterior cingulate, parahippocampus, and lateral temporal cortex towards encoding success. We also wanted to see if connectivity information, including directional connectivity as quantified with mutual information, improved classifier performance above within--site oscillatory information. Finally, we wanted to test nonlinear machine learning-based classifiers and new strategies for reduction of dimensionality for input data. We used a unique database of 21 stereo EEG UTSW patients all of which contributed electrodes from the same core temporo-parietal brain locations. This unique dataset allowed us to test classifier performance on subjects contributing similar information from on to the next and then report the fraction of individuals in which a given metric improved success. We show that an approach using support vector machines performs better than logistic regression, and we apply new methods of dimensionality reduction that outperform principal components analysis. We used SVM with a non-linear kernel which helps in solving the problem of separating the data which cannot be easily classified by a linear classifier such as Logistic regression. The uniqueness of this method is that during the classification process is that it minimizes the cost function at a unique global minimum. The resulting learning algorithm is an optimization algorithm using Lagrangian multipliers rather than a greedy search. In only 2

subjects did hippocampal connectivity information improve classifier performance; in the remained it was slightly worsened compared to using oscillatory power alone. We discuss applications of our findings in responsive stimulation and place our results within the context of existing literature.

Disclosures: **A. Arora:** None. **B.C. Lega:** None. **S. Segar:** None. **D.S. Rizzuto:** None.

Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

Location: Halls A-C

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Program#/Poster#: 170.17/TT25

Topic: H.02. Human Cognition and Behavior

Support: Toulouse University Hospital

Title: Trapping memory recall using electrical brain stimulation in epileptic patients

Authors: *J. CUROT[1,2], L. VALTON[1,2], M. DENUELLE[2], J.-C. SOL[2], C. BENAR[3,4], J. PARIENTE[2,5], F. BARTOLOMEI[4,3,6], E. BARBEAU[1]
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Abstract: Recall of long-term memories and more precisely ecphory (recollection of a past event cued by a trigger, such as a picture or an odor) are difficult to reproduce experimentally in the lab. However some epileptic patients can experience reminiscences after direct electrical brain stimulation (EBS). Transient “brain states”, which can be assimilated to ecphory, can then be isolated and “trapped” using intracerebral EEG recordings. These recordings are a unique and precious tool to explore long-term memory mechanisms.
Previous results suggest that the recollection of vivid memories after EBS of the cortex may rely on wide networks of brain areas that transiently synchronize and which would include the hippocampus, the perirhinal cortex, but also extra-temporal structures such as the visual cortex. Theta oscillations may play a major role in this synchronization. However, only a few case-reports support these results. We have already demonstrated that EBS to the medial temporal lobe (MTL), especially the perirhinal cortex, is the major gateway to memory networks. But the other components of these networks are only partially known. For instance, the role of the lateral temporal cortex, but also of the insula, which is thought to be involved in subjectivity, or of the posterior cingulate involved in self-related processes, have never been studied in this context. We hypothesize that these reminiscences require the synchronization in the theta band of extra-

temporal regions which are different according to the nature of the memory recalled. More precisely, the lateral temporal cortex, the insula and the posterior cingulate should be part of these networks according to the nature of the memory recalled and should transiently synchronize with the MTL.
To test this hypothesis, we collected the largest series of reminiscences induced by EBS of the medial temporal lobes during stereo-EEG: 22 reminiscences (self-related: 8 personal semantics, 2 episodic memories, 1 reminiscence of a dream; or not self-related: 10 reminiscences related to familiar objects, 1 semantic memory) in 7 epileptic patients. Non-linear correlation EEG analyzes were used to isolate transient activated networks, using broadband EEG signals but also EEG filtered in different frequency bands (from delta to gamma). We compared these reminiscences to 21 EBS leading to a feeling of strangeness or déjà-vu (devoid of any content) and to 26 control EBS (no clinical symptom after EBS in the same regions, with the same frequency and intensity ranges).
Specific networks for these different kinds of reminiscences are found. We are currently analyzing how many types of specific networks we can find.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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Max Planck Society: Max Planck research group grant (to RGB)

Title: Integrating distributed knowledge for future simulations: the ventromedial prefrontal cortex as a hub of brain-wide connectivity

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Abstract: Humans often imagine hypothetical episodes that they may experience in the future. For example, we can envision meeting a personally familiar person at a specific place for the first time. Previous studies have shown that such episodic simulation is based on a core network of brain regions that includes the ventromedial prefrontal cortex (vmPFC). Here, we further test the hypothesis that the vmPFC supports episodic simulations by integrating knowledge about the

elements of the episode (e.g., the person and the place). Given that such information is likely to be distributed across the brain, we predict that the vmPFC serves as a hub of whole-brain functional connectivity during episodic simulation. Furthermore, this should be more pronounced when there is more information to be integrated. To test these predictions, we re-analyzed the data of a fMRI study (Benoit, Szpunar & Schacter, PNAS, 2014) in which participants were asked to imagine episodes involving people and places. Critically, across trials, this study manipulated how much information participants could integrate by varying how familiar they were with the respective person and place. We parcellated the brain using the Brainnetome atlas (Fan et al., Cereb. Cortex, 2016) and - using beta series correlations - constructed connectivity matrices separately for simulation and non-episodic control trials as well as for trials with high and low levels of familiarity of people and places. These matrices were used to estimate the hubness of each brain region by calculating its betweenness centrality (i.e., the fraction of all shortest paths in the network that contain a given region). As predicted, we find that parts of the vmPFC display greater betweenness centrality during episodic simulation versus the control task, and that this property was stronger during simulations comprising combinations of people and places that were more familiar. Follow-up analyses revealed that this enhanced centrality partly reflects a reorganization of the direct connections of the vmPFC. In support of the hypothesis, these findings thus indicate that the vmPFC contributes to episodic simulation by acting as a functional hub that integrates distributed knowledge.

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Poster

170. Memory Modulation: From Stimulation to Functional Connectivity

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NARSAD

Title: Distinct neuronal populations for recognition memory and categorization in the human medial frontal cortex

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Abstract: Decision making relies on the accumulation of evidence in favor of a particular choice. While this process is relatively well understood for perceptual decisions, little is known about decisions that rely on internal representations. Here, we tested two types of decisions that depend on two types of an internal representation: a recognition memory (depends on declarative memory) and a categorization decision (depends on high-level visual representations). We operationalized categorization and recognition memory, respectively, by asking “Is this an image of a car” and “Have you seen this image before?”. We recorded from 242 neurons in amygdala and hippocampus (MTL), and 249 neurons in dorsal anterior cingulate cortex and pre-supplementary motor area (MFC) in six neurosurgical epilepsy patients. Subjects were shown single images of objects from 4 categories and asked to respond to one of the above two questions (in blocks of 40 trials). Subjects gave yes/no responses with button press or a saccade. Accuracy was higher on the categorization trials (97.8 ± 0.6%) than the memory trials (72.7 ± 1.4%), and memory trials were ca. 300ms slower than categorization trials (1.24s ± 0.02, and 0.94s ± 0.03 respectively, $p<1e-22$, 2-sample t-test). Neuronal responses were indifferent to response modality, but showed strong segregation with respect to other factors. In MFC, we identified 79 cells that signaled the choice made (yes or no) only on the memory (n=59/79), the categorization (n=25/79), or both trials (n=5/79). By contrast, visually selective neurons in the MTL were insensitive to task condition (63 cells; Ω^2 effect size = 0.08±0.01) and instead maintained their selectivity across both task conditions (sign test, p=1). MFC cells that encoded memory-based choices showed strong modulation of their spike-field coherence with local field potentials recorded in the MTL, but only when making a memory-based decision. By contrast, the MFC cells that signaled categorization-based choices showed no modulation of spike-field coherence. Our findings show that (i) there are distinct populations of cells in the MFC encoding recognition memory or categorization based choices, (ii) visually-selective MTL cells are insensitive to such task conditions, and (iii) spike-field coherence between field potentials in the MTL and action potentials in the MFC are enhanced based on task demands and may thus facilitate integration of memory-based information to make decisions. These results suggest that memory representations are conveyed from the MTL to the MFC, and that specific neuronal populations within the MFC may then abstract category membership from such memory representations.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Support: JSPS KAKENHI Grant Number JP15K16386

Title: Neural substrates of hierarchical processing in strategic reasoning and language: An fMRI study

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Abstract: Grasping hierarchical relationships is an important human capacity underlying cognitive abilities such as understanding others' actions in complex situations. Language processing, especially sentence comprehension, also involves building hierarchical syntactic structures from incoming word strings. It is unclear, however, whether the neural substrate of hierarchical processing in language overlaps with that in inferring others' actions. To examine whether these neural substrates are common or distinct, we performed an fMRI experiment. Participants underwent two cognitive tasks in separate fMRI sessions: the strategic reasoning (SR) task and language comprehension (LC) task. In each SR trial, subjects saw a picture with two persons playing a strategic game. In this game, one player (the treasure hunter) tried to choose the right button to open a treasure box, while the other player (the enemy) tried to interfere with him/her. The enemy was disguised as a friend and instructed the treasure hunter to press the wrong button. In the without-alarm condition, the treasure hunter was unaware the opposite player was the enemy and failed to open the treasure box. In the with-alarm condition, conversely, the treasure hunter noticed and could circumvent the enemy. Participants were required to infer which button players would press. Since the with-alarm condition entails hierarchically higher-order reasoning than the without-alarm condition, we examined neural correlates of hierarchical reasoning by comparing the with-alarm condition to the without-alarm condition. The same participants also underwent the LC task, where a Japanese sentence was visually presented in each trial. Two syntactic constructions were used in the task: hierarchically more complex double-nested sentences and simpler single-nested sentences. These sentences described situations of the SR task and were carefully controlled regarding semantics. Brain regions involved in hierarchical syntactic processing were identified by comparison between constructions. We found that the bilateral cerebellum, precuneus, and dorsomedial prefrontal region were selectively activated for the hierarchical inference of others' actions, whereas the activation of the left inferior frontal gyrus and left dorsal premotor cortex was common in the SR

task (with-alarm versus without-alarm) and the LC task (double-nested versus single-nested). This shows that the neural substrates of hierarchical processing are partially distinct in reasoning and language domains.

Disclosures: **T. Iwabuchi:** None. **T. Inui:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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BIH Berlin Institute of Health

Title: A neural signature of malleability: General intelligence correlates with ventral striatal activation and epigenetic markers of dopamine neurotransmission

Authors: J. A. KAMINSKI[1], M. RAPP[2], F. SCHLAGENHAUF[1], S. AWASTHI[1], H. WALTER[1], B. RUGGERI[3], G. SCHUMANN[3], S. RIPKE[1], *A. HEINZ[1]
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Abstract: General intelligence has a substantial genetic background in children, adolescents, and adults, but environmental factors also strongly correlate with cognitive performance as evidenced by a strong (up to one SD) increase in average intelligence test results in the second half of the previous century. This change occurred in a period apparently too short to accommodate radical genetic changes. It is highly suggestive that environmental factors interact with genotype by possible modification of epigenetic factors that regulate gene expression. This modification might as well be reflected in recent observations of an association between dopamine-dependent encoding of reward prediction errors and cognitive capacity, which was modulated by stress exposure. Here we show in a cohort of 1475 young healthy human subjects of both sexes from the IMAGEN sample, that general IQ in adolescents is associated with 1) a polygenic score for intelligence in children, 2) functional activation elicited by temporarily surprising reward-predicting cues, and 3) epigenetic markers for dopamine neurotransmission. With respect to components of general IQ, fluid IQ was associated with striatal functional activation, and crystallized IQ more strongly correlated with the genetic score and epigenetic markers. Our results demonstrate a neurobiological correlate of the malleability of general IQ and point to the importance of epigenetic mechanisms influencing dopamine neurotransmission. Peripheral epigenetic markers are in need of confirmation in the central nervous system and should be

tested in longitudinal settings specifically assessing individual and social stress factors that can modify epigenetic structure.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Title: Neural correlates of discounted subjective value track heroin use in treatment-seeking opioid users

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Abstract: Objective: Increased impulsive decision-making has been widely observed in individuals with substance use disorders. Several studies have pointed to brain regions in the valuation network as necessary computational neural substrates for this behavior, and posited that dysfunction in this circuitry in drug users might be at the basis of these disorders. Although identifying these regions is important, more pressing and clinically relevant questions remain unanswered: how does this dysfunction relate to the severity of drug use? And, in the case of treatment-seeking individuals, how does it relate to treatment success/failure, i.e. concomitant use, relapse and dropout? Focusing on the current opioid epidemic, we addressed these questions by following a cohort of patients with Opioid Use Disorder (OUD) receiving pharmacologic and psychosocial treatment, and assessing their neural activity in a temporal discounting (TD) task at 2 time points over the course of their treatment. Critically, this longitudinal approach allowed us to follow their dynamics in symptomatology, drug use and impulsivity and test how our neural measures relate to recovery or treatment failure.
Methods: We conducted 2 fMRI sessions in OUD patients starting standard outpatient treatment (~4 and ~12 weeks post treatment entry). Patients completed a TD task in the scanner in which

they were asked to choose between immediate and delayed monetary rewards. Patients' symptoms, drug use (by self-report and toxicology) and impulsive decision-making were assessed during the fMRI sessions and in multiple separate sessions over the course of 7 months. fMRI and behavioral testing was also performed in a cohort of matched community controls. Results: In preliminary results (n=9), we find similar task-based activation of valuation circuit areas, e.g. ventromedial prefrontal cortex and posterior cingulate cortex, across both OUD patients and controls. Interestingly, in OUD patients, dorsolateral prefrontal cortex (DLPFC) subjective value coding for delayed rewards decreased as a function of recent and imminent heroin use. Our results point to a role for DLPFC recruitment as a contributor to success in treatment for OUD and suggest it could be a potential candidate area for therapeutic intervention. Current efforts in this study focus on increasing our sample size and establishing whether neural activity elicited by our task is truly predictive of future drug use, relapse and dropout from treatment.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Title: An imbalance in neural subjective value signaling and connectivity within the brain's valuation circuit underlies heroin use vulnerability in humans

Authors: *A. B. KONOVA[1], S. LOPEZ-GUZMAN[1], A. URMANCHE[1], S. ROSS[2], K. LOUIE[1], J. ROTROSEN[2], P. W. GLIMCHER[1]
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Abstract: Rates of heroin misuse have skyrocketed in recent years. Although much progress has been made on the front of public health efforts to tackle this issue, there is a surprisingly limited basic understanding of the disease in humans. We recently showed that week-to-week changes in computational markers of decision making—and risk preferences in particular—are proximately tied to illicit heroin use in individuals seeking treatment for their opioid addiction. These data suggest that the value of risky prospects is enhanced when these individuals are most vulnerable. In the present study, we sought to examine the neurobiological basis of this vulnerability. We

collected multi-band functional MRI data on a risky decision making task and at rest in opioid users starting outpatient treatment. The same fMRI protocol was repeated 8 weeks later to assess for therapeutic changes due to treatment. We continuously tracked subjects' illicit heroin use, treatment status, and risk preferences between, and before and after, the two scans. Given the position of the ventromedial prefrontal cortex (VMPFC) and striatum as central nodes in the brain's valuation circuit, and given that exposure to heroin produces pathological dopaminergic signaling in these regions, we hypothesized value coding in these regions and connectivity between them, indexing circuit-level dynamics of the valuation circuit, will underlie an individual's vulnerability to use heroin. In preliminary data (n=16), we found that heroin use did not disrupt value coding in either region (based on a comparison of opioid users to matched community controls). As in health, the VMPFC and striatum carried the subjective value signal necessary for choice of the risky prospects. However, we found that (1) enhanced value coding in the striatum (caudate) and (2) diminished value coding in the VMPFC both correlated with imminent heroin use (within a week), suggesting an imbalance within the valuation circuit might better account for drug use vulnerability than individual regions' activities alone. In direct support of such an imbalance, we further found (3) weakened resting-state connectivity between the VMPFC and striatum was an even stronger predictor of heroin use. Our ongoing work is focused on examining if successful treatment reduces heroin use by restoring this imbalance (at 8 weeks relative to treatment entry), with the broader aim of contributing to the basic understanding of opioid addiction in humans and to the development of neuroscience-informed intervention strategies.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Title: Personal core values modulate risky choice evaluation and subsequent risk-taking behavior: An fMRI study

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Abstract: Human core ideological values and risk-taking preferences are important aspects of human mental functions that influence decision behaviors and subsequent outcomes. Theoretically, core values might drive risk-taking preferences during stimulus evaluation and action selection, in terms of neuropsychological processes. Nevertheless, the neural correlates underlying the relationship between core values and risk processing are not clear. In this study, we evaluated how two specific core values (hedonism and security) modulated risk-taking decisions and the associated functional neural responses during risky choice evaluation. We hypothesized that hedonism and security should serve as an accelerator and a brake for risk-taking, respectively. Forty healthy adults (mean age (SD): 23.1 (2.0) yrs; 16 males) underwent a Lottery Choice Task (LCT) functional magnetic resonance imaging (fMRI) experiment. In each trial, magnitude (1~110 points) at stake and the probability of winning (or losing) (4% ~ 95%) the stake were shown. Participants decided whether to accept or decline a stake given, and then outcome feedback (win or loss) was provided. Five EPI runs were acquired per participant, each with 218 volumes [TR=2s; 38 axial slices; 3.4375 x 3.4375 x 4 mm resolution]. Core values were assessed using the Schwartz Value Survey (SVS).Behavioral data was analyzed by generalized linear mixed-effects models (GLMMs) with Markov chain Monte Carlo(MCMC) stimulation. Behaviorally, higher regard for security was associated with lower LCT acceptance rate ($\beta = -0.38$, $p < .05$) ,and the effect was more evident with increasing likelihoods of losses ($\beta = -0.91$, $p < .05$). Also, acceptance rate increased with hedonism for trials with higher likelihoods of losses and lower costs ($\beta = 0.35$, $p < .05$). For brain responses, higher regard for hedonism correlated with increased neural sensitivity to the interaction between probability x magnitude across left parietal and bilateral frontal regions ($p<.05$ with FDR correction for multiple comparisons). Simple slope analysis revealed that neural sensitivity to probability in these brain areas increased with increasing hedonism only under low magnitudes. No reliable effects of security on LCT neural function were observed. Our findings suggest that hedonism might drive elaborative neural processing when stimuli match their reward-seeking ideological goal vis-a-vis attention and control-related brain areas. By contrast, the neural correlates underlying security-related effects on decision behavior might involve more diffuse computations.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Title: The use of contextual information in uncertain value-based choices

Authors: *V. MAN, W. A. CUNNINGHAM
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Abstract: A critical question in decision neuroscience is concerned with how individuals make choices when faced with uncertain information (Rushworth & Behrens 2008). While we know that the brain employs cognitive maps when making value-based choices (Daw et al., 2005), the degree to which these contextual details can substitute for impoverished stimulus information in the decision process remains relatively unexplored. In two experiments, we explore the mechanisms that underlie the degree to which individuals draw from context to inform uncertain choices.

In experiment 1, healthy adults (n = 40) were instructed to match one of two shapes to a cue. Upon a successful response, one shape was associated with monetary gain and the other shape the prevention of monetary loss. Critically, on 50% of trials the cue was obscured, such that participants could not rely on stimulus-driven information for choice. However, all trials were nested within reward contexts for which the gain and loss outcome magnitudes may be asymmetrical, such that participants could reply on contextual information to determine the optimal choice. We predicted that the proportion of choice for the high-magnitude option versus the alternative would be highly skewed in asymmetrical contexts. Surprisingly, though we found a slight choice proportion bias based on contextual magnitude information ($R^2 = 0.155$), this did not differ significantly from symmetrical (uninformative) contexts. However, there was a significant interaction between context and response reaction time on uncertain trials ($p=0.008$), driven by faster choices for the loss prevention option when contextual demands favored loss prevention ($p>0.001$).

Experiment 2 sought to explore the neural bases of this contextual influence on value. A separate cohort of healthy adults (n=40) performed the same task during fMRI scanning. When we specified block-level regressors that aggregated across trials within a context but differentiated context types, contrasts between contexts that favored gain versus loss revealed regions associated with regulatory control processes, including the anterior cingulate and dorsolateral prefrontal cortex (Botvinick & Cohen, 2014). Importantly, representations of greater contextual loss value further engaged the bilateral insula, and informative versus uninformative contexts uniquely further engaged the medial prefrontal cortex. Together these experiments demonstrate potential mechanisms driving the use of contextual information in value-based choice, and suggest a prioritization towards loss aversion with choice uncertainty.

Disclosures: V. Man: None. **W.A. Cunningham:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Title: Evidence for a neural bottleneck in the transformation from objective value to subjective utility

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Abstract: Motivated behavior is predicated on subjectively evaluating the worth of available options, often integrating information across multiple dimensions. It is assumed that each of these dimensions has an independent influence on the final subjective valuation. For example, when considering an option consisting of two apples and an orange, your preferences for the orange should not alter your preferences for the apples. Here, we show that this basic assumption is incorrect - providing evidence that simultaneous value-to-utility transformations produce interference. Further, the nature of this interference reveals the format in which value-to-utility information is encoded within the brain.

Recently, we localized value-to-utility information to the dorsal anterior midcingulate cortex (daMCC, Kurnianingsih and Mullette-Gillman, 2016). We localized initially using gains and then independently replicated using losses. Two critical results lead to the current study: 1) value-to-utility information for both gains and losses converged in the daMCC, and 2) preferences for gains and losses were uncorrelated across the sample (a result replicated across multiple recent studies, in and out of this lab). These two results present an intriguing question - what happens when two different value-to-utility transformations occur simultaneously? Based on studies of neural information processing in sensory and motor systems, the co-occurrence of two signals will result in interference in the computations - such as an averaging of the produced percept (for example, see Nichols and Newsome, 2002).

Subjects (134) engaged in a two-alternative choice task with 436 interleaved trials, selecting between a certain monetary value and gambles composed of either gains, losses, or both [A, B, or A+B]. All gambles featured a possible zero to provide a consistent frame across trials.

Four risk preferences were calculated independently - gains-pure (GP), losses-pure (LP), gains-mixed (GM) and losses-mixed (LM). Structural equation modeling replicated no significant correlation between GP and LP and high correlations within domains (GP to GM and LP to LM,

r~.6). Critically, after accounting for preference covariance from pure trials, we find a very high correlations between the GM and LM risk preferences (*r*~-.7). This relationship emerges due to the simultaneous processing of two independent value-to-utility transformations.
Further, examining the specific form of the relationship between GM and LM, we see that it is compatible with the averaging of linear-multiplicative value modulation signals, but not with a power function representation (i.e., power function alpha).

Disclosures: O.A. Mullette-Gillman: None. **Q. Lee:** None. **M. Cheung:** None. **Y.A. Kurnianingsih:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

Support: The Research Fund for the Doctoral, Beijing Nova Program (Z141107001814042)

Collaboration Between Clinical and Basic Research in Capital Medical University (16JL09)

The Capital Applied Clinic Research Programs of Science and Technology (Z131107002213171)

Title: Multiple loci of value comparison independently distributed in the brain

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Abstract: The neural mechanism of economic decisions remains obscure. Converging evidence in neuroimaging currently has reached to a broad consensus that ventromedial prefrontal cortex (vmPFC) plays a critical role in value comparison. However, as the expected value of each option could be extensively encoded in the brain, it remains doubts why value comparison should necessarily take place in a specific locus. Here we used multiple stereo-electroencephalography (sEEG) on the epilepsy patients (n = 10) to explore the regions could be involved in value comparison, while the subjects made choices from two value options that were sequentially presented. We found that the gamma-band (50-90 Hz) electrical signals were correlated with value difference between the two options in the regions of intra-parietal sulcus (IPS), dorsolateral Prefrontal cortex (DLPFC) and medial Obitofrontal cortex (mOFC). The

value-specific gamma-band signals emerged after the presentation of the later option. Alternatively, the beta-band (15-30 Hz) electrical signals in some of these regions rebounded after decision-making, and were correlated with the absolute value difference, which was associated with decision uncertainty. Furthermore, The gamma-band and beta-band electrical signals appeared independent across these regions, as they were no apparent correlations specifically associated with the tasks. Surprisingly, there were no electrical signals associated with value difference in vmPFC. Taken together, our findings revealed that value comparison might not take place in vmPFC, but in other multiple regions, where option values were also encoded. Furthermore, value comparison could be carried out in parallel in multiple regions and independently in each local region.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

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Program#/Poster#: 171.09/TT36

Topic: H.02. Human Cognition and Behavior

Title: Computation of value representations when choosing among attractive faces

Authors: *N. FURL
psychology, Royal Holloway, Univ. of London, Egham, United Kingdom

Abstract: A great deal of research has examined the brain circuitry contributing to decision making in the context of non-social primary rewards (e.g., juice) and secondary rewards (e.g., money). We investigated more social decisions - which face is most attractive - using functional magnetic resonance imaging. In a trinary choice task, participants chose between two highly attractive “target” faces and a third, unattractive, “distractor” face. Choices between the two attractive targets (which competed for choice) were associated with posterior visual areas, posterior cingulate, parietal cortex and dorsolateral prefrontal cortex. Replicating previous behavioral findings, choice behavior showed greater sensitivity to target value differences when distractors were unattractive, reflecting divisive normalization of target value representations. This behavioral effect was associated with responses in bilateral motor areas and visual occipitotemporal cortex. Our findings show that value computation and comparison when choosing attractive faces reflect a network of visual, parietal and frontal areas.

Disclosures: **N. Furl:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

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Yale FAS Imaging Fund

Title: Neural mechanisms underlying effortful persistence

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Abstract: The adaptive adjustment of behavior in pursuit of desired goals is critical for survival. To accomplish this complex feat, individuals must weigh the potential benefits of a given course of action (e.g., food, safety from predators) against time, energy, and resource costs. Prior work in this domain has greatly advanced understanding of the cortico-striatal circuits that support motivated goal pursuit, characterizing core aspects of subjective valuation. However, these complex dynamic calculations have traditionally been examined at discrete points, for instance evaluation and choice. How time and effort costs are integrated in persistence is less well understood. When persistence has been examined, it has primarily been limited to the temporal domain, leaving the mechanisms underlying individual differences in the dynamic updating of effort requirements during goal pursuit poorly understood. Utilizing tasks that better map onto the dynamic nature of naturalistic goal pursuit may allow us to characterize the neural mechanisms underlying variable success in goal achievement across individuals and contexts. In the present ongoing study, participants underwent functional MRI (fMRI) while completing a novel paradigm to examine willingness to exert physical effort to obtain monetary rewards or avoid punishments. Preliminary results suggest that effortful persistence varies within and between individuals, with trait impulsivity tracking total task earnings (up to $13). Willingness to exert effort in pursuit of rewards recruited a broad network of cortico-striatal and cognitive control regions, including the medial prefrontal cortex, dorsal anterior cingulate cortex, and ventral striatum. Ongoing timecourse analyses aim to identify neural signals that associate with effort costs. fMRI data will be analyzed for ramp-like signals that are modulated by number of button presses. By revealing how willingness to exert physical effort is instantiated and updated in the brain, the current study can inform how effort cost weighting impacts goal pursuit and achievement.

Disclosures: L.M. Patrick: None. **K.M. Anderson:** None. **A.J. Holmes:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: ONR MURI grant (N00014-16-1-2832)

McDonnell Foundation award

Title: Investigating the cost of cognitive effort

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Abstract: Cognitive effort is usually aversive, which is evident in people's tendency to avoid cognitively demanding tasks. Brain imaging studies have observed that cognitive effort is correlated with decreased responses in reward circuits but increased activity in the cognitive control network. Thus, the 'cost of control' hypothesis suggests that effort costs derive from the demands a task places on cognitive control systems. A further corollary is that these same systems contribute both to the experience of effort during a task and decisions based on future expectations of effort. Finally, as individuals differ in their sensitivity to effort, these differences must derive from differences in the cognitive control system. Here, we test 1) the cost of control hypothesis in relation to individual differences in effort avoidance and 2) the premise that effort prediction during task selection and effort experience during execution are supported by a common system. We parametrically manipulated the level of effort during fMRI scanning by increasing cognitive control demands during a demand-selection paradigm, separately optimizing for effort selection and execution. In a sample of 52 participants, we found widely variable individual differences in overall demand avoidance, a rate that was larger than prior behavioral studies. A follow-up study compared Need for Cognition (NfC) Inventory scores between behavioral vs. fMRI volunteers. Behavioral volunteers scored lower in NfC than fMRI volunteers, and explained the variation observed in fMRI participants. A behavioral procedure was used to divide fMRI participants into Demand Avoiders and Demand Seekers. Consistent with the cost of control hypothesis, frontoparietal cortex (FPC) activity linearly increased, and reward network activity linearly decreased with increasing effort in the entire sample. However, the change in selection rates across effort levels could not be predicted by the change of activity in either network, but by the inhibition of a task-negative brain network (Default Mode Network; DMN) only in Demand Avoiders. Moreover, average connectivity between FPC and DMN predicted overall selection of the easier task. Finally, inconsistent with assumptions in the prior literature, the brain networks that tracked the anticipated effort level during a decision differed from those tracking effort execution. In conclusion, this study obtained partial support for the

cost of control hypothesis, while also highlighting the role of task-negative brain networks in modulating individual differences in effort avoidance behavior.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Program#/Poster#: 171.12/TT39

Topic: H.02. Human Cognition and Behavior

Support: NIH K12HD073945

Title: Fatigue acts on the behavioral and neural representations of effort valuation

Authors: *P. S. HOGAN[1], S. X. CHEN[2], V. S. CHIB[3]
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Abstract: Everyday life is filled with decisions about how much and what types of effort we are willing to exert. Of the various factors that could affect these choices, fatigue (both natural and pathological) has the potential to significantly impact how we value effort costs. In this experiment, we investigate how behavioral preferences for prospective effort, and associated neural activity, change when an individual is placed in a physically fatigued state. To accomplish this we scanned participants with fMRI while they performed an effortful task requiring force production via a hand-clench dynamometer. Participants first learned an association between exerted force and a numerical scale ranging from zero to one-hundred relative to the individual's maximum voluntary contraction. To estimate subjective preferences for the effort involved in our task, participants performed a series of risky forced-choices involving two potential options for prospective effort - a low amount of effort, required with certainty; or a risky option that could result in even more effort exertion or none at all (with equal probability). These 'effort gambles' were presented under two conditions: a non-fatigued choice phase, wherein participants only had to make decisions about prospective effort. This was followed by a fatigued-choice phase, beginning after an initial fatiguing block, where effort gambles were interspersed with smaller blocks of physically demanding repetitions of grip force exertion. We found that participants exhibited an increase in the convexity of their subjective effort cost functions from the pre- to post-fatigued state, indicating that fatigue has an effect of increasing the marginal costs associated with the task as more effort is required. A total of 30 subjects have been scanned and subsequent analyses will examine brain regions that display activity associated with changes in subjective valuation of physical effort costs.

Disclosures: **P.S. Hogan:** None. **S.X. Chen:** None. **V.S. Chib:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: NSF Grant 1658303

Title: The cognitive chronometry of rapid human decision making

Authors: ***M. D. NUNEZ**, J. VANDEKERCKHOVE, R. SRINIVASAN
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Abstract: Our goal is test theories about the time-course of quick human decision making using model-based cognitive neuroscience approaches with measured neural processes. The chronometry of participants' neural behavior was explored by finding stimulus-onset and motor response event-related potentials (ERPs) as measured by the electroencephalogram (EEG). The chronometry of participants' decision-making cognition was estimated by finding Bayesian posterior distributions of diffusion model parameters, a model-type that explains both accuracy and reaction time behavior. Both neural measures and behavior were used in hierarchical Bayesian model-based cognitive neuroscience approaches to separate reaction times into three components: visual encoding, decision-making, and motor response, resulting in both participant-level and single-trial level estimates of these time periods in milliseconds. Visual encoding times were estimated with known evoked EEG responses to visual stimuli (N1 latencies, negative ERP peaks over parietal electrodes around 200 milliseconds). Motor response times were estimated using response-locked, motor-related EEG potentials (early and late motor evoked potential latencies and mu and beta rhythm desynchronization time-courses over central electrodes). Decision-making time was estimated by the subtraction of visual encoding and motor response time from reaction times and then compared to posterior distributions of decision-making time as estimated by drift-diffusion models of human behavior. Out-of-sample prediction of new EEG measures and reaction times was used to verify the cognitive interpretations of these EEG measures when embedded in cognitive models.

Disclosures: **M.D. Nunez:** None. **J. Vandekerckhove:** None. **R. Srinivasan:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Program#/Poster#: 171.14/TT41

Topic: H.02. Human Cognition and Behavior

Title: The influence of distractor interference and stimulus ambiguity on neural indices of performance monitoring

Authors: *P. J. BEATTY[1], J. R. FEDOTA[2], D. M. ROBERTS[1], C. G. MCDONALD[1]
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Abstract: Empirical and theoretical research suggests that the frontocentral N2 component of the event-related potential indexes the magnitude of response conflict (Yeung et. al, 2004; Yeung & Cohen, 2006). In the present study, we explored whether the N2 and other indices of conflict monitoring are similarly affected by distractor interference and stimulus ambiguity. To this end, EEG was recorded while participants performed a modified version of the Erikson flanker task, in which the degree of similarity between flanker and target stimuli was manipulated. Preliminary analyses demonstrate that when flankers were dissimilar to targets, the expected congruency-dependent neural and behavioral signatures were observed. Specifically, N2 amplitude was greater and response times were longer for incongruent trials. In addition, P3 latency was longer for incongruent trials, suggesting that stimulus evaluation was delayed in this condition. By contrast, when flankers were similar to the target, there were no congruency-dependent differences in N2 amplitude, P3 latency or response time. However, N2 amplitude and P3 latency for trials in which stimuli were ambiguous differed from congruent, but not incongruent trials in which flankers were dissimilar to the target. In addition, the error-related negativity (ERN) was significantly reduced for error trials in which stimuli were ambiguous, which would be expected for data limited errors (Scheffers & Coles, 2000). This pattern of results is consistent with the notion that both stimulus ambiguity and distractor interference can induce response conflict, and that these sources of response conflict share the same neural underpinnings. However, the possibility remains that the N2 may instead index increased activation of the performance-monitoring network when task demands are elevated.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

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Yale Interdepartmental Neuroscience Program

China Scholarship Council

Title: Medical decision making under uncertainty: Behavior and neural correlates

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Abstract: Uncertainty is ubiquitous in real-life decisions, and individual attitudes towards it often influence the ability to reach optimal decisions under critical situations. Previous neuroimaging studies of decision making under uncertainty mostly focused on the monetary domain. Although a few studies looked at other rewards (e.g. food, water), the neural basis of decision making in more complex and abstract domains is not well characterized. Choosing medical treatment is one of the most important decisions we make and involves high level of uncertainty. To investigate individual attitudes towards uncertainty in medical decisions and their neural basis, we had 16 human participants (ages 29.5±7.9, 9 females) make medical and monetary decisions in a functional MRI experiment. In the medical task, participants were asked to imagine that they were injured and lost the motor function of their legs. On each trial, participants chose between a fixed treatment with a certain outcome of slight improvement, and an experimental treatment with chance of better improvement but also chance of no effect. The experimental treatment varied in the degree of improvement it offered, and in the level of uncertainty. In the monetary task, participants chose between a fixed monetary gain and a lottery with chance of a higher gain, but also chance of no gain. For both medical and monetary tasks, the outcome probability of the uncertain option was fully known in half of the trials (risky trials), but only partially known in the other half (ambiguous trials). Behaviorally, attitudes towards risk and ambiguity were not correlated across participants either in the medical (r = 0.047, p = 0.86) or monetary (r = -0.15, p = 0.57) domains. Participants were averse to ambiguity in both domains ($p < 0.01$ in medical domain, $p < 0.05$ in monetary domain, two-tailed, one sample t test). The degree of aversion in the medical domain was correlated with that in the monetary domain (r = 0.66, $p < 0.01$) and the magnitudes of the two were not significantly different (p = 0.28, two-tailed, paired t test). A whole-brain analysis revealed higher activation in the right

inferior temporal cortex and the parahippocampal gyrus during medical decisions compared to monetary decisions, potentially reflecting increased memory demands of the medical task. A parametric analysis using each participant's subjective ratings of the treatment outcome levels identified brain regions, which have been previously implicated in value representation, including a focus in the insula. These preliminary results suggest the existence of both domain-specific and domain-general neural mechanisms for valuation and decision making.

Disclosures: R. Jia: None. **L. Ruderman:** None. **T.R. Fried:** None. **I. Levy:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: NIH 2T32MH067564

NIH/NIDCD R01DC010014

Title: Neural and behavioral expression of human olfactory fear generalization

Authors: *D. B. PORTER, L. P. QU, E. GJORGIEVA, T. KAHNT, J. A. GOTTFRIED
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Abstract: Stimulus generalization is a fundamental cognitive mechanism that underlies adaptive behavior. Behavioral generalization has been studied in various species, but few human studies have addressed this topic, and even fewer have targeted the olfactory system. We have developed a novel fear conditioning/generalization paradigm to characterize olfactory generalization at behavioral and neural levels in the human brain. 27 healthy subjects have completed behavioral discrimination training and generalization test sessions during functional magnetic resonance imaging (fMRI). A total of 11 odor mixtures, ranging between two pure odorants, were created for each subject. In addition to these mixtures, two conditioned stimuli were also created; one odor mixture (CS+) was intermittently paired with mild shock while another odor mixture (CS-) was never paired with shock. Using an aversive conditioning paradigm, subjects first learned the association of CS+ odorant with shock and performed with over 85% accuracy. Subjects then underwent fMRI scanning during test sessions, where all 11 mixtures were presented (excluding CS+ and CS-), and indicated by button press whether the delivered odor was previously associated with shock or not. These responses were used as an index of olfactory generalization. We have found that olfactory behavioral generalization is robust, peaking in the direction of the CS+, away from the CS-. In addition to identifying a behavioral peak shift, we present implications for physiological peak shifts. Reaction times and sniff volumes are lower for the

peak shifted odor (PK) than for mixtures surrounding the CS+, implying the transfer of the salient association of the shock from the CS+ to the PK. The perceptual dynamics of our olfactory peak shift resemble what has been described for visual orientation (Kahnt, et al. 2012), and suggest that the olfactory system may engage similar mechanisms. The combination of behavioral, psychological, and neural measures collected in this study will help gain insight into mechanisms underlying olfactory generalization. These findings can bring new understanding to future studies in post-traumatic stress disorder and help direct new treatments that target brain networks supporting peak shift modes of generalization.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Collaborative Research Project (2016-2804) of the Brain Research Institute

Collaborative Research Project (2017-2804) of the Brain Research Institute

Title: Endogenously initiated movements are preceded by neural activities in multiple cortical regions: an event-related fMRI study

Authors: *H. SAKATA[1], K. ITOH[1], Y. SUZUKI[1], K. NAKAMURA[2], M. WATANABE[1], H. IGARASHI[1], T. NAKADA[1]
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Abstract: In the classical view of human behavior that underlie behaviorism or stimulus-response theory, a stimulus input triggers a chain of neural activities in the brain to culminate in behavior output. However, an action can also be initiated endogenously in the brain without an external stimulus, the neural mechanisms responsible for which remain incompletely understood. This fMRI study investigated the neural origins of self-initiated behavior, by identifying brain regions that increased in neural activities several seconds before self-initiated movements occurred. Subjects performed a hand grasping task under two conditions: free timing condition and cued timing condition. In the free timing condition, subjects chose their own moments to make the grasping movements, and, in the cued timing condition, they made the movements in response to an externally given visual stimulus. As a result, supplementary motor area (SMA)

began to activate as early as ten seconds before self-initiated movement (accounting for the hemodynamic delay), representing a blood oxygenation level dependent (BOLD) signal correlate of the readiness potential of electroencephalogram, referred to here as “readiness BOLD signal.” Significant readiness BOLD signal was observed also in precuneus, right inferior parietal lobule, right middle frontal gyrus/inferior frontal gyrus, and insula, which have been known to contribute to internally generated behavior, but with no prior evidence for such early and slow accumulation of neural activities. Moreover, visual and auditory cortices also exhibited clear readiness BOLD signals with similarly early onsets, even in the absence of external stimulation.Slow accumulations of neural activities in distributed cortical areas, including sensory, association, and motor cortices, underlie generation of self-initiated behavior. The finding suggests reconsideration of the current prevalent view that SMA or some specific locus in frontoparietal cortex serves as the single most important neural origin of self-initiated movement.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

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Program#/Poster#: 171.18/TT45

Topic: H.02. Human Cognition and Behavior

Title: Why do irrelevant option matter? An fMRI-TMS study of context-dependent preferences

Authors: *H.-K. CHUNG[1], T. SJÖSTRÖM[2], H.-J. LEE[3], Y.-T. LU[4], F.-Y. TSUO[5], T.-S. CHEN[7], C.-F. CHANG[8], C.-H. JUAN[9], W.-J. KUO[3], C.-Y. HUANG[6]
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Abstract: In standard rational choice theory, decision-making is represented as assigning value to each feasible options and choosing the option with the highest value. Moreover, the value of an option should depend only on its intrinsic properties, not on the context in which it appears. However, both humans and animals are known to exhibit a violation of rationality known as "decoy effect": introducing a clearly worse option (a decoy) can influence valuation of other options in the same choice set. Exactly how and why decoys trigger this effect is poorly understood and the mechanism of control process to overcome this decision bias is not known. We used functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation

(TMS) to investigate the neural underpinning of the decoy effect and the control system in the human brain. Our experimental design allows us to test the neural activity differences between the same two options in the different choice sets consisting of different decoys. We used an additive utility function having different weights for each attribute to model the intrinsic utilities of each options. The weights were estimated using choices having only two available options from post-tests. The left ventral striatum was more active when the chosen option dominated the decoy (compared with when the same chosen option did not) while behaviorally the same option was chosen (same values of intrinsic utilities). This suggests that the decoy may make the valuation of relevant option more attractive even when choices appear fully rational. The RT difference in consistent matching pairs supports this presumption. The RT reduced in the trials that chosen option dominated the decoy, indicating that it was indeed easier to make a decision in this situation even though choice stays the same. Consistent with the idea that control is recruited to prevent from producing biased choices, the right inferior frontal gyrus (rIFG), often implicated in inhibiting prepotent responses, connected more strongly with the striatum when subjects successfully overrode the decoy effect and made unbiased choices (compared with when they were not successful). This is further supported by our TMS experiment: subjects whose rIFG was temporarily disrupted made biased choices more often than a control group. These findings point towards a role for neuroscientific discoveries in shaping long-standing economic views of decision making.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: SFI grant 15/CDA/3591

Title: Electrophysiological and behavioural indices of decision bound adjustments across contexts of weak and strong evidence

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Abstract: Detecting target events in a noisy sensory environment can be facilitated by accumulating evidence over time up to a bound, i.e. a criterion amount for which one is willing to commit to reporting a positive detection. This bound is believed to be under strategic control,

and adaptable to behavioral context. Extensive behavioral modeling and neurophysiological work has examined bound adjustments across contexts of accuracy versus speed emphasis. However, other important contextual factors, such as how strong the target evidence is expected to be, have not been systematically examined. Here we consider a task scenario where subjects continuously monitor a noisy, incoherent dot motion stimulus and are rewarded for making a timely button-click to report detection of intermittent, coherent-motion targets of a fixed, 1-second duration, but incur a loss for false alarms or misses. In a context where target evidence is known to be strong, it makes sense to set a high accumulation bound that fully avoids false alarms - bound-crossings due to inter-target noise alone - while comfortably detecting all targets. In a context with low evidence strength, because cumulative evidence builds more slowly within the limited target timeframe, the bound should be set lower to catch the weaker targets, which must be traded against increased false alarms. Here we conducted computational modeling and electrophysiological analysis to establish that humans do indeed shift their decision bound in this way. The 'CPP', a centroparietal positive event-related potential previously shown to trace accumulation-to-bound dynamics in continuous decision tasks, reached lower pre-response amplitudes when all targets in a block were 25% coherence than when all targets were 70%, consistent with a lowered bound. Model fits indicated that RT distributions, hit and false alarm frequencies were best explained by continuous, leaky accumulation to a bound that was significantly lower for weaker evidence. In a control condition where both evidence strengths were mixed in the same block, CPP buildup rate and hit rate scaled with coherence in the same way as in the unmixed blocks, but crucially, CPP amplitude did not differ, nor did false alarm rates, confirming that these bound-adjustment effects were truly an effect of context rather than simply of physical evidence strength. Because the mixed-coherence control block was always run last, we observed additional, interesting effects of practice, where faster detection RTs were accompanied by steeper CPP buildup and a stronger early, posterior negativity ('N2') recently implicated in low-level detection of evidence onsets.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Support: DFG grant TR-SFB134 C05

Title: Food-specific hypothalamic up-regulation of valuation signals after sleep deprivation

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Abstract: Reduced nocturnal sleep is associated with an increased risk of obesity, as demonstrated by correlations between sleep duration and percent body fat or change in body mass index. Neuroimaging studies revealed up-regulated neural reactivity to visual food stimuli after sleep deprivation (SD) or restriction in reward-processing areas such as the anterior cingulate cortex, ventral striatum and insula. However, previous studies did not take into account subjective reward values of the presented food stimuli, lacked behavioral measures or collection of circulating hormone concentrations. We rigorously tested the association between SD and food cue processing using high-resolution fMRI. After taking blood samples from thirty-three lean, healthy participants, they underwent high-resolution fMRI while performing a value-based decision making task with snack food and trinket images following a full night of habitual sleep (HS) and a night of SD in a randomized, within-subject design. We found that total and des-acyl ghrelin concentrations were increased after SD compared with HS (log total ghrelin: SD: 6.98 ± 0.07 pg/ml, HS: 6.89 ± 0.06 pg/ml, $t(30) = 2.04$, $p = 0.05$; log des-acyl ghrelin: SD: 6.68 ± 0.09 pg/ml, HS: 6.50 ± 0.10 pg/ml, $t(29) = 2.32$, $p = 0.03$; log acyl ghrelin: SD: 5.50 ± 0.10 pg/ml, HS: 5.58 ± 0.09 pg/ml, $t(30) = -1.01$, $p = 0.32$). Despite similar hunger ratings due to fasting in both sessions (SD: 4.42 ± 0.32, HS: 4.12 ± 0.34, $t(32) = 0.84$, $p = 0.41$), participants were willing to spend more money on food items only after SD (state x category interaction: $F(1,32) = 5.83$, $p = 0.02$). Furthermore, functional MRI data paralleled this behavioral finding, revealing a selective increase in hypothalamic valuation signals in response to highly rewarding snack food images only after SD (right hypothalamus: (x/y/z) = (4/-1/-10), $t = 3.44$, $p_{FWE} = 0.02$; left hypothalamus: (x/y/z) = (-4/-7/-12), $t = 3.33$, $p_{FWE} = 0.03$). Beta estimates of these two hypothalamic peaks were not correlated with ghrelin concentrations (all ps > 0.14). These results demonstrate that SD enhances brain activity in homeostatic key structures selectively for rewarding food and thus suggest underlying neural mechanisms for the link between obesity and reduced sleep.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

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Topic: H.02. Human Cognition and Behavior

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Oklahoma Center for the Advancement of Science and Technology (OCAST) HR10-141

The William K. Warren Foundation

Title: Shared and unique brain activations involved in pleasantness and self-control inferences about foods

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Abstract: Previous electrophysiological and neuroimaging research has identified the role of the dorsal mid-insula in the primary experience of taste, as well as the homeostatic consequences of food stimuli. In addition, it has been shown that the mid-insula's response to tastes is modulated by their reward value, potentially due to its connectivity to striatal and orbitofrontal reward circuitry. Psychiatric illnesses with associated changes in appetite and eating behavior, such as depression and anorexia, also present with differential mid-insula responses to visually-presented food stimuli. These various lines of evidence suggest a key role for the mid-insula in food motivation and food-related decision making. However, comparatively little is known about the involvement of the dorsal mid-insula in the moment-to-moment decisions about what to eat. Sixty healthy subjects viewed pictures of various appetizing foods during fMRI scanning. While viewing the pictures, subjects alternated between providing two types of ratings: how pleasant it would be to eat the depicted food at the present moment, or how much self-control it would take to not eat that food at the present moment. Imaging data was analyzed using parametric regressors that incorporated subjects' pleasantness or self-control ratings. Group-level analyses thus identified regions of the brain where the response to food pictures was modulated by subjects' moment-to-moment inferences of the pleasantness or self-control associated with specific foods. Whole-brain conjunction analysis identified that both food pleasantness and self-control judgments involved overlapping regions of activity throughout the brain, including virtually all of the brain's classical reward regions. A contrast of the two conditions, however, revealed distinct cortical networks preferentially responsive to each condition. Food pleasantness judgments resulted in greater involvement of somatosensory and motor regions, whereas self-control judgements involved the preferential activation of fronto-parietal control regions. Notably, food pleasantness and self-control judgements exhibited opposing effects upon the activation of the dorsal mid-insula. The activity of the dorsal mid-insula increased with participants' ratings of food pleasantness, but decreased with participants'' ratings of the self-control required to abstain from eating a food. This suggests that behavioral control of eating involves not only the recruitment of executive control brain regions to guide behavior, but the inhibition of cortical sensory regions involved in processing the hedonic and homeostatic value of food stimuli.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Title: Ultra high gamma codes choice options in delay discouting

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Abstract: In mammals the value of a reward decreases as a function of time: the longer the delay to the reward the stronger the reward is discounted. Hence a smaller but sooner (SS) reward over a larger but later (LL) reward is preferred. Studies on delay discounting (DD) comprehensively look on neuronal signatures of decisions in the brain like dopamine fluctuations in the Nucleus Accumbens or neural activation in the ventral striatum or lesions to the orbitofrontal cortex. How the brain evaluates choice options comparing these with a subjective preference signal is unknown. In our study subjects decided between 10€ in 1,3,5,11,24 or 52 weeks (LL) or a smaller amount immediately (SS). We adjusted SS amounts after each decision to estimate the indifference point for each temporal interval of the LL option. In a first sample of 13 subjects we measured decision times (DT). Subjects decided on average within 2.3 sec with no DT differences between SS and LL choices (p=.11) assuming that in SS choices subjects did not respond impulsively but evaluated choice options similarly. A second sample of 18 subjects used a fixed interval of 3 sec (to reduce motor activity) to ponder choice options while whole-head magnetoencephalographic activity was recorded. We found significant amplitude reduction in the theta/beta range (6-35Hz- bilateral parieto-occipital distribution), significant amplitude increase in the gamma range (50-70Hz with MEG sensor clusters in a mid central and left fronto-temporal region) and a significant amplitude decrease in an ultra-high gamma (uHG: 150-330Hz right fronto-temporal region). 140 to 650msec following choice presentation the amplitude of uHG discriminated between the 6 different delays to the 10€ payoff with strongest amplitude decrease when SS and LL choice options were separated by only 1 week. Between 570 and 885 msec the amplitude of the uHG correlated with the difference between SS and LL monetary amounts. The gamma band showed amplitude differences between SS and LL choices in two intervals. Mid central MEG sensors showed an early difference within 140 msec following choice presentation, silencing during choice evaluation by uHG and increased in fronto-temporal gamma sensors afterwards. Gamma preference signal and uHG choice evaluation are integrated by means of cross frequency coupling with pronounced modulation of correlation between both frequency bands by the phase of theta/beta activity starting around 2 sec following the presentation of the choice options. In sum, uHG evaluates the temporal and monetary difference

of choice options sequentially and is integrated with a preference signal before humans finish their decision.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Program#/Poster#: 171.23/TT50

Topic: H.02. Human Cognition and Behavior

Support: McDonnell Foundation Collaborative Award (#220020387); Kiwanis International Funding

Title: Impaired congruence between preference and choice following damage to the ventromedial prefrontal cortex

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Abstract: A well-documented effect of focal damage to the ventromedial prefrontal cortex (vmPFC) is a deficit in decision-making that can be notoriously difficult to detect using standard neuropsychological tests, and yet is plainly evident in the real-world behavior of individuals suffering these lesions. A core feature of this deficit may be a deficiency in "internal consistency" during social decision-making – that is, impaired congruence between preferences and choices. To explore this idea, we designed a laboratory task to measure internal consistency. Sixteen individuals with focal vmPFC lesions (vmPFC group), 16 brain-damage comparison individuals (BDC group), and 16 normal comparison individuals (NC group) completed a three-option forced-choice preference task using three sets of attributes, each associated with one option, as the basis for their choices. Options and attributes were either social (selection of a spouse) or non-social (selection of a house) in nature. Participants also completed visual-analogue ratings to indicate how much they liked each of the options, and rated the influence of the individual attributes on making a decision. Internal consistency was defined as the percent of trials in which the chosen option was also the most preferred option in that trial. The most preferred option was determined both by the average attribute ratings of sets and by visual analogue ratings.
The BDC and NC groups never differed significantly from one another in the analyses and so were combined into a non-vmPFC group. A 2 x 2 mixed design ANOVA with group as the between-subjects factor and stimulus type as the within-subjects factor revealed that mean internal consistency between choices and preferences derived from averaged attribute ratings

was significantly lower in the vmPFC group (M = .67) compared to the non-vmPFC group (M = .75) in the social condition ($p\eta^2$ = .09). There was no significant difference between the two groups in the non-social condition. An exploratory Fisher's Exact test on the internal consistency between choices and visual-analogue preference ratings revealed that a greater proportion of individuals in the vmPFC group (10.4%) were internally inconsistent on at least one social condition trial compared to the non-vmPFC group (4.2%).
These results suggest that internal consistency during social decision-making may be deficient among patients with focal vmPFC damage and that this deficit can be measured empirically despite its elusive nature in the real world. These findings are consistent with previous research demonstrating discrepancies between social-cognitive abilities and behavior among patients with focal vmPFC lesions.

Disclosures: **M.D. Bowren:** None. **K.E. Croft:** None. **J. Reber:** None. **D. Tranel:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01-DA029149

Title: Individuals with ventromedial prefrontal damage have unstable, but fundamentally transitive preferences

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Abstract: If you prefer going to SfN in Washington, D.C. over San Diego, and San Diego over New Orleans, then logically you should prefer SfN in D.C. over New Orleans. Preferences having this property are transitive, and being transitive in one's choices is crucial for advancing one's interest in an optimal manner (von Neumann and Morgenstern, 1947). Studies of preferences in individuals with focal damage to the ventromedial prefrontal cortex (vmPFC) have found them to make more intransitive choices (Fellows and Farah, 2007; Henri-Bhargava et al., 2012; Camille et al., 2011), suggesting a crucial causal role for the vmPFC in a fundamental aspect of value representation. However, these past studies simply count any instances of intransitive choice, without accounting for the fact that decision-making can be probabilistic and noisy. Thus, these cannot distinguish whether patients are fundamentally intransitive (i.e., they would make transitive violations consistently, always making the same error), or are merely more unstable (causing momentary errors) while maintaining transitivity over all. To distinguish between these possibilities, choice pairs need to be repeated multiple times, which allows testing

whether underlying preferences are stable while allowing for probabilistic or noisy deviations. In the present study, we tested 13 individuals with vmPFC damage, 10 patient controls with dorsomedial or dorsolateral damage, and 20 healthy, age and education-matched controls. In this task, participants made choices in three categories: artwork, chocolate bars, and gambles. Ten pairs of options in each category were presented repeatedly throughout the experiment, intermingled with 55 other pairs that are presented only once. When considering the non-repeated choices, we replicate previous studies by finding that individuals with vmPFC damage make more total intransitive selections relative to healthy controls over all domains, and more errors relative to both healthy controls and patient controls in the artwork domain. Looking at the repeated choices, however, revealed that in all cases individuals with vmPFC damage were simply noisier overall (i.e., their choices were more unstable), rather than being fundamentally intransitive. That is, all of our participants made choices consistent with models that assumed a transitive ordering plus noise or variability. These results suggest that individuals with vmPFC damage may be noisier and more variable in their choices than controls, perhaps due to a more unstable momentary value representation, but their underlying preferences retain transitive ordering.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

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Title: Distributed temporal processing in human prefrontal cortical neurons during cognitive control

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Abstract: Our everyday lives require monitoring our environment for relevant cues, ignoring irrelevant ones, and adjusting expectations based on outcome. These cognitive control processes are thought to arise in the prefrontal cortex, particularly in the dorsal anterior cingulate cortex (dACC). Cognitive control processes have been correlated with modulations of frontal midline theta (4-8 Hz) power in numerous EEG studies. Here we examine single neuron recordings and local field potentials (LFP) from the human dACC (136 neurons from 6 subjects; both dACC and dlPFC LFPs) and dorsolateral prefrontal cortex (dlPFC; 367 neurons from 9 subjects; only dlPFC LFPs) recorded from neurosurgical patients performing a Stroop-like task with both spatial and flanker sources of cognitive interference. We examined firing rate in each area using a generalized linear model (GLM) with factors: cognitive interference, response identity, feedback valence, and a nuisance variable for reaction time. We found sparse rate coding of conflict in both dACC and dlPFC with relatively low proportions of significant cells (N = 14 in dACC (9%) and N = 15 (4%) in dlPFC). Temporal codes were more prevalent in both dACC and dlPFC, as measured with spike field coherence (SFC). dACC units exhibited significant increases in SFC with theta and beta range LFPs in both medial (beta: N = 54; 38%. theta: N = 37; 29%) and lateral PFC (beta: N = 46; 34%. theta: N = 63; 46%). These neurons also exhibited significant phase codes in these two frequencies, suggesting dACC is rhythmically entraining a broad prefrontal network. A majority of dlPFC exhibited significant SFC with theta range LFPs (52%), yet exhibited reduced coherence with beta range LFPs and did not exhibit a phase code. Large (> 100), simultaneously recorded populations of these cells also exhibited a temporal code for conflict and predicted reaction time on a single trial basis. Together these data illuminate the neuronal coding of cognitive control in the human prefrontal cortex, suggesting a mechanism in which rate coding recruits and binds large populations of neurons into a multiplexed temporal code which binds task elements together over time.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 171.26/TT53

Topic: H.02. Human Cognition and Behavior

Title: An acute bout of aerobic exercise increases metabolism at the prefrontal cortex as determined by optical brain imaging data while subjects perform Stroop test

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Abstract: INTRODUCTION: Both exercise physiology and neuroscience literature shows that physical exercise can improve cognitive functioning. Hemodynamic responses from prefrontal cortex (PFC) has been correlated to executive functions. OBJECTIVES: The goal is to determine which hemodynamic responses (cardiovascular or neural) recorded from the prefrontal cortex (PFC) are correlated with a decision-making task. HYPOTHESIS: An increase in cardiac output (with an acute bout of aerobic exercise) would alter the cardiovascular hemodynamic responses corresponding to the decision-making task. METHODS: Human subjects were recruited to perform two different color-word Stroop tests (identifying the word and not the color) — congruent and incongruent, while brain activities in the PFC were recorded simultaneously using optical near infrared spectroscopy (NIRS) imaging. The measures were the relative changes in concentration of oxy-hemoglobin (oxy-Hb) (representing oxygen delivery) and deoxy-Hb (representing oxygen extraction). Plus, the total cerebral blood volume (oxy-Hb + deoxy-Hb), and cortical oxygenation (oxy-Hb - deoxy-Hb) were computed. The experimental protocol was repeated before and after 30 minutes of aerobic exercise on an elliptical cardiovascular exercise machine at 70% of the maximal heart rate. In order to separate exercise effects from practice effects, the same paradigm was repeated with 30 minutes of sedentary activities (non-exercise) instead of exercise. RESULTS: Our preliminary results showed that the hemodynamic changes in the PFC are task-responsive for both the congruent and incongruent Stroop tasks. With exercise the diff-Hb (cortical oxygenation) showed a significant ($p<0.05$) increase in 10 subjects. CONCLUSION: This supports the hypothesis that an increase in cardiovascular activity could alter the cognitive processing as evidenced by the metabolic changes in the hemodynamic responses at the PFC.

Disclosures: A. Pal: None. **N.D. Tam:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: RSF 14-18-02522

Title: Cathodal tDCS over pMFC reduces post-decisional preference change

Authors: *M. COLOSIO, A. SHESTAKOVA, V. KLUCHAREV
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Abstract: Objective: Normative decision theory suggests that our choices reflect our preferences whereas the theory of "cognitive dissonance" postulates that our choices shape our preferences (Festinger, 1957). For example, when individuals choose between two equally attractive items, they are more likely to devaluate an unselected item. In order to reduce the inconsistency caused by cognitive dissonance, individuals re-evaluate the alternatives. Previous fMRI (Izuma et al. 2010), TMS (Izuma et al., 2015), and EEG (Colosio et al. 2017) research indicates that the posterior medial frontal cortex (pMFC) is the key region involved in post-decisional preference change. However, the pMFC function in cognitive dissonance remains unclear. Here, we used cathodal transcranial direct-current stimulation (tDCS) to interfere with pMFC activity during difficult choice making in order to probe its causal role in post-decisional spreading of alternatives.
Methods: 17 right-handed healthy participants took part in the study, where they performed a modified version of free-choice paradigm (Izuma at al., 2010). Firstly, participants rated their preference for food items using an 8-point Likert scale (Preference task I). Then, 20-minute cathodal tDCS of the pMFC was delivered. Next, participants were asked to choose between pairs of items that were equally evaluated in the Preference task I (Difficult trials induced high degree of dissonance) or pairs of two differently evaluated items (Easy trials induced low degree of dissonance). Finally, participants rated the initial set of items again (Preference task II) to detect post-decisional spreading of alternatives (PSA). Importantly, each participant received both real and sham stimulation separated by a 1-week interval. Additionally, two control conditions were included to the free-choice paradigm.
Results: We found a significantly smaller PSA in Difficult trials ($F_{(1,16)}=4.651$; $p < 0.05$) after the real tDCS than after sham stimulation. We found no effect of tDCS on PSA in Easy trails.
Conclusion: The pMFC has been previously associated with the choice-induced preference change. Recent findings also have demonstrated the causal role of pMFC in error/conflict processing, including attitude change after difficult choices. Our results show that post-decisional preference changes (PSA) following conflicting choices are significantly reduced by tDCS over the pMFC applied prior to choices. Therefore, we provide further evidence of a causal role of pMFC region in choice-induced preference changes.

Disclosures: M. Colosio: None. **A. Shestakova:** None. **V. Klucharev:** None.

Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: UCI Startup Grant IR/GU13780

Title: Hippocampal encoding of causal confounding

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Abstract: As scientists, we are keenly aware that if putative causes always co-occur, the independent influence of neither can be estimated: This “no confounding” constraint, fundamental to philosophical and statistical approaches to causation, is at the core of scientific inference. Intriguingly, a substantial behavioral literature suggests that naïve human reasoners, adults and children, are similarly sensitive to causal confounding. The current study used functional magnetic resonance imaging to investigate neural substrates mediating the detection of causal confounding and its differentiation from other sources of uncertainty, such as the stochasticity of the outcome. While being scanned, participants studied and made judgments about the influences of various fictitious allergy medicines on headache (a side effect). Three target medicines (A, P and X) always occurred in combination with a respective alternative medicine and the probability of headache given a particular treatment was either 1.0 (+), 0.5 (±) or 0.0 (-): In the “confound” condition, both the target and alternative medicine always co-occurred, followed by headache (AB+); in the “independent” condition, the target medicine always occurred in combination with an alternative medicine that also occurred on its own (PQ+, Q-); finally, a “stochastic” condition was identical to the “independent” condition, except that headache occurred with a probability of 0.5, rather than 1.0, in the presence of the medicine compound (XY± , Y-). On each of several trials, participants made predictions, and received feedback, about the presence of headache given that a particular medicine, or combination of medicines, had been administered. In addition, frequent queries regarding the causal strength of each individual medicine were distributed intermittently throughout the task. Results suggest that the posterior hippocampus, an area previously implicated in uncertainty detection, discriminates between causal confounding and independence, as well as between deterministic and stochastic causation.

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Poster

171. Decision Making and Reasoning: Value and Effort-Based Decisions

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Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01 MH 095894

Title: Can foraging behavior shed insights on depression? Using LFPs, EEG and eye tracking in conjunction with a patchy foraging task to establish biomarkers for depression

Authors: D. BERKAY[1], *A. RAMAKRISHNAN[2], M. L. PLATT[3]
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Abstract: With over 350 million sufferers according to the WHO depression is the largest cause of disability as measured by years lost. Understanding the neurobiological mechanisms underlying depression could help establish biomarkers that would aid early identification and guide preventive measures to remediate before development of more severe symptoms. In this study, we utilized a version of the explore-exploit dilemma called the patchy foraging task to study depression. Lack of will and motivation associated with depression predict impairments in explore–exploit decision-making, specifically that individuals with depression will exploit more and explore less than optimal. Participants and nonhuman primate (NHP) performed the foraging task in which they foraged for berries across different patches depicted on the computer screen. The number of visible patches conveyed the richness of the environment. When the current patch was selected, participants were awarded some points, which translated into monetary reward at the end of the session. The NHPs were provided a juice reward. For every subsequent choice of the same patch, the points/ juice awarded decreased. When they decided to leave the patch, they arrived at the new replenished patch after an associated travel time (5s or 20s). Although the number of bushes was unlimited, the total time was limited. The marginal value theorem provides a normative framework to quantify optimal performance in the task and specifies that foragers should leave when the reward rate falls below the average for the environment. Depression scores were ascertained using standard scales (BDI and CESD). Pupil size and blink rate were monitored using Eyelink 1000 (SR Research, Ltd.). EEG recordings were obtained using a modified Epoc+ (Emotiv, Inc) wireless EEG device. In NHPs, LFPs were recorded from rostral ACC using a linear array (LMA, Microprobes). Preliminary results indicate that behavior of humans (n=6) and monkeys (n=1) was near-optimal. Patch leave times in the rich environment were significantly shorter than in the poor environment. Individual differences in leave times were correlated with human participants' depression scores, which in turn were correlated with resting state frontal theta power. Pupil diameter, EEG, and LFPs accurately forecast the onset of an explore choice. Foraging behavior can be used as an assay for impaired decision making in depression. By capturing participants' behavior with a normative model, a mechanistic link between pupil diameter, EEG, LFP and behavior can be established, which may help understand the factors driving deviations from optimality and establish neural biomarkers in depression.

Disclosures: D. Berkay: None. **A. Ramakrishnan:** None. **M.L. Platt:** None.

Poster

172. Social Cognition

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 172.01/TT57

Topic: H.02. Human Cognition and Behavior

Title: The impact of individuation on the bases of human empathic responding

Authors: *J. E. KIAT, J. E. CHEADLE
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Abstract: While there is substantial overlap in the neural systems underlying empathy for people we know as opposed to strangers, social familiarity has been shown to significantly moderate the empathic neural responses towards the negative experiences of others. Intriguingly however, variance in empathic neural responses towards known and unknown targets has not been reflected by behavioral differences as indexed by empathic ratings. One explanation for this disconnect is that empathic evaluations of known and unknown individuals draw on different bases (e.g. target identity, target reactions) within the empathic process. To test this hypothesis, we utilized high density EEG to assess how individuating targets with personal names moderated the link between behavioral pain ratings and attentional processing oriented towards (a) initial target processing and (b) subsequent expressions of discomfort by the target. Consistent with prior findings, no differences in pain ratings between individuated and unindividuated targets was observed. However, individual differences in pain ratings for individuated targets was strongly predicted by attentional processing levels, as indexed by the P300, during the initial presentation of those targets, a relationship absent for unindividuated targets. In contrast, pain ratings for unindividuated targets was related to levels of attentional processing, as indexed by the Late Positive Potential (LPP), during the subsequent discomfort expression stage. Furthermore, the LPP response to individuated target discomfort was linked to behavioral measures of emotional expressivity whereas the LPP response to unindividuated target discomfort was linked to cognitive appraisal. These findings indicate that individuation can significantly shift the bases of empathic responding.

Disclosures: J.E. Kiat: None. **J.E. Cheadle:** None.

Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: DAAD

Title: Reciprocity of social influence

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Abstract: It has been shown that humans use advice from other humans in order to improve their decisions. To this end they integrate their own and their partner's evidence taking into account the reliability of their information. At the same time, social interactions are subject to reciprocity, for example in the case of trust, people are more likely to trust those who trust them. Yet, whether social influence and advice taking is reciprocal remains an open question. To address this question, we designed an experiment in which human subjects needed to solve a perceptual decision making task together with a virtual partner. Both the human player as well as the virtual partner first made an initial decision independently and then were allowed to revise their initial decision on the basis of the initial decision of the other player. Finally, the revised decisions of both players were revealed. Participants were made to believe that the virtual partner was another human subject participating in the experiment. We manipulated the amount of influence that the virtual partner took from the participants. Our result show that humans were more strongly influenced by their partner, if they had reciprocally more influence on the decisions of their partner. We then repeated the experiment telling subjects that their partner is a computer. This time the reciprocity of influence on the decision disappeared. These findings can be interpreted in the sense that humans use reciprocity to communicate in social decision making.

Disclosures: A. Mahmoodi: None. **B. Bahrami:** None. **C. Mehring:** None.

Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: Grant-in-Aid for JSPS Research Fellow #268054

Title: Social modulation of foraging behavior in humans: using the patch-use paradigm

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Abstract: Optimal foragers should maximize gain per cost. According to the "optimal patch use model" proposed by Charnov (1976), when an animal exploit a food patch, optimal stay time for the patch can be calculated as the maximization of the net rate of energy intake per foraging time (= search time + stay time). Therefore, when the search time for a patch is longer, the optimal stay time in the present patch should be longer.
However, this classical patch use model postulates solitary foraging. When animals forage in a group, some foragers ("scroungers") can get a free ride on other foragers who search and find food ("producers"). Social foraging theory (Giraldeau and Caraco 2000) predicts that foraging in a group lead individuals to leave patches earlier than solitary foraging, because of (1) shorter search time by scrounging and (2) decreased gain in a patch due to competition. In spice finches, patch use time was actually shortened by social foraging (Beauchamp and Giraldeau 1997).
We tested the prediction in humans using a computer game mimicking patch exploitation. The participants were required to search and exploit food patches hidden in a virtual foraging space. Because (as in natural settings), participants should make "stay or leave" decisions and sequentially encounter and leave patches. Each participant experienced solitary, social (paired), and again solitary foraging conditions. In the social condition, food patches could be shared by two participants. Thus, "producer-scrounger" structure could be emerged.
As we predicted, patch stay time was shorter in the social condition. However, contrary to our prediction (1), shorter search time did not predict shorter stay time. Furthermore, to test the prediction (2), another set of participants played the game in pairs but patches for each individual were distinct; i.e. there was no competition in a patch and "producer-scrounger" structure could not be emerged. Even in this population, patch stay time also shortened in the social condition. Contrary to the predictions from social foraging theory, even without direct interference between individuals, non-specific social facilitation by "mere" presence of a co-forager caused shorter patch time.

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Poster

172. Social Cognition

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Program#/Poster#: 172.04/TT60

Topic: H.02. Human Cognition and Behavior

Title: Neural mechanisms underlying self-consistency in social behavior

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Abstract: Social factors influence on our behavior in a profound way, such that we conform not only with the behavior of others but even with the behavior of ourselves because we want to appear consistent. However, the neural mechanisms of self-conformity remain unclear. In this study, we used a sequential facial attractiveness-rating task and functional magnetic resonance imaging to investigate the neural mechanisms underlying self-conformity and compare them against group conformity. Participants performed the task in the scanner three times in total. First, participants were asked to rate 360 female faces for facial attractiveness one by one. Second, a week later, participants were asked to rate the same faces again. At the second rating, participants were provided with a previous rating of either the "group average" or "yourself". We manipulated each participant's previous ratings by splitting them into two conditions; true (same rating as their previous rating) or false (shift above or below their previous rating), both for group and individual ratings. Self-conformity and group conformity were measured as change in ratings from previous to second rating. Finally, 2-7 days later, we asked the participants to come back to the scanner and rate the same faces again, without reminder as in the first rating to assess the temporal stability of conformity. Participants adjusted their judgments at the second rating to conform to both previous own and group rating. However, these conforming attractiveness ratings returned to the initial ratings at the third rating. Thus, both self-conformity and group conformity occurred temporarily in our task and both conformity effects disappeared entirely in several days. In the brain, we found that activation in medial prefrontal and central orbitofrontal cortex were specific to self-conformity; on the other hand, activation in temporo-parietal and hippocampal regions were specific to group conformity. These results suggest that self-conformity and group conformity require dedicated neural machinery and are based on distinct neural mechanisms.

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Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: DARPA W31P4Q12C0166

NSF IIP 1215327

JUMP Foundation

Title: Deconstructing neurodynamic information flows in healthcare teams during simulation training

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Abstract: An information-organization approach was developed for detecting and quantitating the fluctuating neurodynamic organizations in teams. Neurodynamic organization is the propensity of team members to enter into prolonged (seconds-minutes) metastable neurodynamic relationships as they encounter and resolve disturbances to their normal rhythms. Team neurodynamic organizations were detected and modeled by transforming the physical units of each team member's EEG power levels into Shannon entropy-derived information units about the team's organization and synchronization. This transformation from physical units to information units bridges micro level social coordination events with macro level expert observations of team behavior allowing multimodal comparisons across the neural, cognitive and behavioral time scales of teamwork.
The information in the neurodynamic data streams of teams engaged in naturalistic decision making (healthcare (*n=12*) or collaborative problem-solving (*n=11*)) was separated into information unique to each team member, the information shared by two or more team members, and team-specific information related to interactions with the task and team members. Most of the team information consisted of that contained in an individual's neurodynamic data stream. The information in an individual's data stream that was shared with another team member was highly variable being 1-60% of the total information in another person's data stream. From the shared, individual, and team information it becomes possible to quantitatively describe the dynamics of each team member during the task, as well as the neurodynamic interactions

between members of the team.
The innovation of this study is the potential it raises for developing globally applicable quantitative models of both team member and overall team dynamics that will allow comparisons to be made across teams, tasks and training protocols.

Disclosures: R. Stevens: None. **T. Galloway:** None. **A. Willemsen-Dunalp:** None.

Poster

172. Social Cognition

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Program#/Poster#: 172.06/TT62

Topic: H.02. Human Cognition and Behavior

Title: Characteristics of cognitive impairments and their effects on the functional outcome after inpatient rehabilitation in subacute stroke patients

Authors: *Y. KIM, M. SOHN
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Abstract: Objective: To determine the frequency and characteristics of vascular cognitive impairment (VCI) in patients with subacute stroke who underwent inpatient rehabilitation and to analyze whether cognitive function can predict functional assessments after rehabilitation.
Methods: We retrospectively reviewed the medical records of patients who were admitted to our rehabilitation center after stroke from October 2014 to September 2015. We analyzed the data from 104 patients who completed neuropsychological assessments within 3 months after stroke onset.
Results: Cognitive impairments were present in 86 of the 104 patients (82.6%). The most common impairments were in visuospatial function (65, 62.5%) followed by executive function (63, 60.5%), memory (62, 59.6%), and language function (34, 32.6%). Patients with impairments in the visuospatial and executive domains had poor functional assessments at both admission and discharge ($p < 0.05$). A multivariate analysis revealed that age ($\beta = -0.173$) and the scores on the modified Rankin scale ($\beta = -0.178$), Korean version of the modified Barthel Index (K-MBI) ($\beta = 0.489$) at admission, and Trail-Making Test A (TMT-A) ($\beta = 0.228$) were related to the final K-MBI score at discharge (adjusted $R^2 = 0.646$).
Conclusion: In our study, VCI was highly prevalent in patients with stroke. Patients' scores on one of the subtests for executive cognitive function, namely the TMT-A, were highly predictive of their final K-MBI score. Collectively, our results suggest that post-stroke executive dysfunction is a significant and independent predictor of functional assessments.

Disclosures: Y. Kim: None. **M. Sohn:** None.

Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant MH080838

Title: Multiagent social coordination dynamics - from experiment to model

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Abstract: Complex living systems (e.g. brains, social groups) are sustained by virtue of coordination among their many components/agents. Theoretical modelling of multiagent coordination enhances our understanding of a wide range of systems with laws transcending specific levels of description and system types. Existing models of coordination dynamics have focused mainly on systems that are either very small ($N \leq 4$) or very large: for small systems, coordination patterns may be modelled in detail although size limits complexity that typically unfolds on multiple spatiotemporal scales; for large systems, models are usually constructed to fit macroscopic descriptions (such as overall synchronization) but may lack explanatory power across scales, for example their (in)ability to predict system behavior at one scale in response to changes at another. Here we devised new models in order to bridge this divide and to help uncover coordination mechanisms that are consistent across spatial scales. We extended the well-established model of dyadic coordination (Haken-Kelso-Bunz equations, 1985) to systems of arbitrary number of agents by modifying the coupling terms while retaining the agents' intrinsic dynamics (viz. nonlinear oscillators of certain natural frequencies). Three types of coupling were studied: (1) each agent coupled to a mean-field (unweighted); (2) coupling strength from each agent to another weighted by constants; (3) coupling strength from each agent to another adapted to ongoing dynamics where couplings from the same agent to others are in competition. We describe the models' relevance to phenomena observed in a prior experiment (Zhang et al., SfN, 2016). Plausible models should exhibit the following key properties: (1) a critical amount of diversity in agents' natural frequency (δf^*) such that if diversity $\delta f > \delta f^*$, segregated frequency groups coexist in the ensemble, and if $\delta f < \delta f^*$, initially divided groups merge into a supergroup; (2) phase coordination that is mainly metastable (agents intermittently dwelling upon and escaping from particular phase relations); (3) cross-frequency coordination across segregated groups; and (4) coordination in an established group is modified when a new member joins. This work serves as an initial step towards a generalized theory of coordination dynamics invariant to the size and substance of the systems observed. Such experimentally grounded models can serve

as a basis for understanding and restoring complex social and neural coordination, thereby helping to improve mental well-being of individuals who suffer from social isolation or coordination disorders in general.

Disclosures: **M. Zhang:** None. **J.A.S. Kelso:** None. **E. Tognoli:** None.

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Topic: H.02. Human Cognition and Behavior

Support: NIMH Grant MH080838

Title: Fundamental modes of social coordination correspond to specific patterns of correlated neural activity in the virtual brain

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Abstract: Behavioral studies of interpersonal coordination reveal the existence of two fundamental patterns of in-phase and anti-phase locking that correspond to well-known attractors in theoretical models of Coordination Dynamics. When human subjects (H) coordinate with another human or with a virtual partner (VP) programmed to produce an opposite pattern of coordination (or with very weak coupling), additional patterns are observed including a weakly stable phase coordination at ~2.5rad as well as *de novo* patterns promoting the stability of H-VP coordination. Although the emergence and stability of these patterns are well understood, ethical concerns restrict our ability to directly observe and manipulate the underlying neural activity, thus limiting our understanding of the associated neural mechanisms and dynamics. Using the Virtual Brain, a computational platform for multiscale simulations of whole brain dynamics, we investigated different neurobehavioral patterns of social coordination that a virtual subject (VS) might engage in by varying systematically the phase and amplitude difference between the visual input (observation of social partner's movement) and motor output (motor intention). The virtual brain consisted of 76 cortical regions governed by the Stefanescu-Jirsa 3D neural mass equations with intrinsic parameters (μ=0.01, s=4) chosen to secure a robust EEG power spectrum in the 10Hz band. Visual observation of the social partner's movement was represented by a square wave forcing signal to bilateral primary visual cortices while the self-movement was accounted by a similar signal of identical frequency applied to the left motor cortex. We found that behaviorally observed patterns of social coordination corresponded to maximally distinct patterns of correlated neural activity, i.e. patterns with maximum mean Euclidean distance

relative to others. Next, we computed the pseudo-EEG corresponding to the virtual brain network activity and compared the results with experimental data. We found that behavioral patterns locked in-phase, antiphase and with a 2.35rad phase-lag corresponded to specific distributions of 10Hz EEG neuromarkers, resembling some features of experimental data, including mu and alpha oscillations and the phi complex. We conclude that fundamental modes of social coordination entrain spatially distinct patterns of neural activity. Failure to establish these neural patterns may be a precursor to deficits in social behavior. Therefore, this work has implications for the development of novel neuromarkers for diagnosis and treatment.

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Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: the MEXT-Supported program for the Strategic Research Foundation at Private Universities, 2014-2018.

Title: Functional brain networks reflecting human characteristics

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Abstract: (**Introduction**) A human being can be described by diverse human characteristics of feeling, thinking, and behaving. Brain function underlies those characteristics, and thus it is expected to be possible to evaluate the characteristics describing an individual by measuring brain function. Measurement of human characteristics by fMRI usually requires the related tasks to the characteristics but it is very difficult for some characteristics. In this study we attempted to identify functional brain networks of resting state fMRI corresponding to various psychometric variables reflecting human characteristics by which we can describe an individual comprehensively. (**Method**) One hundred sixty college students were participated in the study. We prepared a set of 130 psychometric variables related to social ability, intelligence quotients and emotion quotients. Psychological tests for measuring the psychometric variables and MRI experiments were performed in separate days. For MRI experiments all subjects were scanned by 3T MRI (Siemens) in two sessions that included structural (T1) and functional imaging (resting-state fMRI). Structural images were acquired by MPRAGE sequence. Resting-state fMRI data were acquired by a multiband EPI sequence. (**Results**) Brain areas for the psychometric variables

were identified by the correlation analysis (p = 0.05, corrected), which amounted to 163 brain areas. The ROIs were distributed over the brain regions of frontal, parietal, temporal, occipital, and cerebellar cortices and sub-cortices. Functional networks were identified based on the 163 ROIs. In the analysis, correlation coefficients were calculated between the correlation matrices and the psychometric variables. Networks were identified for a fixed significance level of p = 0.001 (corrected), which had different numbers of edges. To obtain a similar number of edges for every identified network, two thresholds were used; one was a significance level of p = 0.005 (corrected) and the other was the number of edges, namely, around 15 per network. Among 130 psychometric variables, 128 significant functional networks were identified for 116 variables. (**Discussion and Conclusion**) We identified a set of 128 functional networks spanning the human characteristics by rs-fMRI and psychometric variables. This demonstrates that we can identify functional areas or networks of the brain not only by tb-fMRI, but also by rs-fMRI. It also demonstrates that we can evaluate cognition/behaviors and develop biomarkers for a wide variety of human characteristics from a single rs-fMRI scan.

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Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Title: Using a dual-task paradigm to assess the effects of cerebral hemispheric load on attribution judgments

Authors: *K. T. BRENNAN[1], B. JAMES[2], E. M. MOLONEY[2], S. J. E. WONG-GOODRICH[2]
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Abstract: When humans evaluate the causes of negative behaviors in others, situational attributions require more cognitive resources and more elaborate neural processing than that of dispositional (person) attributions (e.g., Kestemont et al., 2013; Reeder, 2013). Consequently, increasing cognitive demands (e.g., simultaneous memory task) during the evaluation of another's behavior can lead to a decrease in situational attributions (reviewed in Reeder, 2013). We were interested in whether implementing a simple motor task to increase hemispheric load would similarly influence attribution judgments. Thus, the current study used a dual-task paradigm to examine whether engaging in a lateralized motor task while reading a fictional passage would alter the degree of subsequent situational versus dispositional attribution ratings about a character's behavior. Right-handed participants silently read a brief passage about a parent's workday and subsequent conflict with the parent's two young children. Gender-neutral

language was used throughout the passage when referring to the parent. There were three between-groups conditions: no dual-task (Control), left-hand dual-task (Left), and right-hand dual-task (Right). Participants in the dual-task conditions repetitively tapped a computer mouse with their left or right index finger while reading the passage. Finger-tapping is primarily lateralized in the contralateral brain hemisphere; thus, tapping required participants to utilize additional hemispheric resources while interpreting the passage. Participants then completed a 7-point Likert-type scale that measured how much a participant agreed with a list of situational and dispositional judgments about the parent's behavior. Higher total scores indicated a greater degree of situational attribution. Analyses showed that compared to the Control and Left groups, attribution ratings were significantly lower in the Right group (*p*s < .01), with no difference between the Left and Control groups. There were no significant differences in reading comprehension scores across the groups, nor in finger-tapping rates during the dual-task conditions. Because language is lateralized in the left hemisphere for most right-handed individuals, these findings suggest that tapping with the right, but not left, hand while reading about another's potentially negative behavior may lessen the probability to make situational attributions due to the increased demand on the left hemisphere. Results may generate questions about the influence of motor tasks (e.g., operating a computer mouse or cell phone screen) that are often used while reading about the behaviors of others.

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Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Title: 'Tis but they name that is (not) my enemy: Reading about benefits of oxytocin does not impact how people categorize others into social groups

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Abstract: Studies of the "seductive allure" of neuroscience information find that explanations of psychological phenomena are more convincing if they include references to brain processes, even if such reductionistic information is irrelevant to understanding the phenomena. This has been demonstrated by changes in subjective ratings of the believability or persuasiveness of the presented material; however, we investigated whether neuroscientific information could produce a change in social behavior, relative to information with a psychological explanation. Due to the

popularity of information about supposed health benefits of oxytocin release, and effects of exogenous oxytocin on social categorization and behavior, the present study was a 2 X 2 between-subjects design in which participants were primed with a fictitious news article touting the benefits of either increasing or decreasing in-group size. These benefits were explained as due to either effects on a psychological construct ("emotional and mental outlook"), or due to increases in oxytocin. Participants then rated a series of individuals that were different from them to varying degrees. Ratings of targets on measures of acceptance and reported similarity were significantly affected by the degree to which they matched the participants' race, religion, and political leaning. However, judgments were not affected by the health benefit information with which they were primed. This is in spite of the fact that participants clearly read and understood the information, as evidenced by visual behavior recorded by an eye tracker, and by near-perfect answers to manipulation check items presented at the end of the study. These findings also contrast with literature on the effectiveness of different kinds of persuasion on judgments of in-group and out-group members. These results imply that experimental effects of oxytocin on social group dynamics may not be influenced by popular reports that invoke names of widely-reported neurotransmitters. Moreover, the persuasiveness of this type of information may have little effect on social categorization, questioning whether the allure of neuroscience information is sufficient to produce real behavior change. This study was preregistered: https://osf.io/r77kb/ Updated material available at: https://osf.io/p9mbn/

Disclosures: M.L. Groft: None. **N.J. Pistory:** None. **R.M. Hardy:** None. **P.J. McLaughlin:** None.

Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant MOP 97821

Title: Mechanistic contributions of the ventromedial frontal lobe to the exploration and recognition of emotional expressions

Authors: *A. R. VAIDYA[1], L. K. FELLOWS[2]
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Abstract: Appropriate social behavior depends on an ability to infer the emotional states of others from expressive cues like facial expressions. Previous work has shown that damage to the ventromedial frontal lobe (VMF) impairs recognition of subtle emotional expressions, and affects fixation patterns to face stimuli. However, the mechanistic role of VMF in emotion

recognition has not been well defined. We tested 37 patients with frontal lobe damage, including 17 subjects with VMF lesions, in a series of emotion recognition tasks with different manipulations of gaze. Subjects were asked to rate neutral, subtle and extreme emotional expressions while freely examining faces, while instructed to look only at the eyes or mouth, and in a gaze-contingent condition that required top-down control of eye-movements to reveal the face stimulus. VMF patients were worse than controls in detecting subtle disgust during free viewing, however fixation patterns did not differ systematically between groups during free or gaze-contingent viewing conditions. Moreover, instructed fixation to the mouth or eyes did not change recognition of subtle fear in patients more than controls. These data argue that VMF is not necessary for normal fixations to face stimuli, and that impairments in emotion recognition may be decoupled from abnormal fixation patterns following VMF lesions.

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Poster

172. Social Cognition

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Topic: H.02. Human Cognition and Behavior

Support: R01 DA036827 to CRR

Title: Topiramate-phentermine combinations as a pharmacotherapy for cocaine dependence

Authors: *A. REYNOLDS[1], W. W. STOOPS[2], J. A. LILE[2], C. R. RUSH[2]
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Abstract: Aim: Cocaine (COC)-use disorder and obesity share common neurobiological substrates. The GABA/glutamate modulator topiramate (TOP) and the monoamine releaser phentermine (PHEN) are effective anorectics that may attenuate the abuse-related effects of COC. A TOP-PHEN combination (Qsymia®) is approved by the FDA, but the efficacy of TOP-PHEN for management of COC-use disorder is unknown.
Methods: In this mixed-model study, the influence of TOP-PHEN combinations on the reinforcing effects of COC is being determined. Separate cohorts of non-treatment seeking, COC-use disorder participants (n=16 completed) are randomized to different maintenance conditions of TOP. Participants in each TOP cohort are maintained concurrently on increasing doses of PHEN (0, 15, and 30 mg/day). After participants in each PHEN cohort are maintained for at least 4 days on each of the PHEN doses, the reinforcing effects of intranasal COC (0, 40, and 80 mg) are determined using a progressive-ratio choice procedure.
Results: COC increased responding on the progressive-ratio procedure during placebo-placebo

maintenance. TOP alone (i.e., combined with 0 mg PHEN) or PHEN alone (i.e., combined with 0 mg TOP) produced moderate, but significant, reductions in responding for COC (i.e., 2.5-4.5 choices). Combining 15 mg/day PHEN with 100 mg/day TOP reduced COC self-administration to the same extent as the constituent drug alone. Combining 30 mg/day PHEN with 100 mg/day TOP produced a large (i.e., up to 7 choices out of 10) and statistically significant reduction in the number of 40 mg COC choices. The TOP-PHEN combinations were well tolerated alone and when combined with COC.
Conclusion: This TOP-PHEN combination (i.e., 100 mg TOP and 30 mg PHEN) decreased COC self-administration by approximately 70%, which is one of the largest reductions observed in a human laboratory study. Efficacy of this TOP-PHEN combination for COC-use disorder should be assessed in a clinical trial. Supported by NIDA grant R01 DA036827 awarded to CRR.

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Poster

172. Social Cognition

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Topic: G.07. Other Psychiatric Disorders

Support: SRG-2-125-14 American Foundation for Suicide Prevention

Title: Classifying borderline personality disorder using resting state functional connectivity: A machine learning approach

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Abstract: Borderline personality disorder (BPD) is characterized by difficulties with self-perception and interpersonal relationships and is associated with self-destructive and impulsive behaviors including suicide (10% incidence). It affects approximately 6% of the population. Currently, diagnostic and prognostic measures of BPD are complicated by the heterogeneity of the BPD psychiatric profile: Individuals with BPD have on average 4 axis I disorders and 1 other personality disorder in their lifetime and there is a large variety of pathological behaviors that fit within BPD. A limited number of studies have investigated the neural pathology of BPD. Structural neuroimaging studies have identified altered volume in every lobe of the brain and multiple subcortical structures, while resting state functional connectivity studies have shown alterations in the frontal lobe, precuneus, and posterior cingulate gyrus. We studied a large heterogeneous psychiatric population including patients with depression, anxiety, substance use, and personality disorders (with high levels of comorbidity). Of a total of 417 patients, 89 were

diagnosed as BPD. The goal was a) To classify BPD patients using machine learning algorithms with resting state functional connectivity data as inputs and b) To identify regions of interest that contribute most to classifying BPD. Inputs were functional connectivity correlations between 117 regions throughout the brain taken from the Automated Anatomical Labeling Atlas. We used 4-fold cross validation and identified the 35 most significant features (t-test) in each of the four folds making up 75% of the data, we then ran the algorithm to classify the cases and controls and validated the algorithm the remaining 25% of the data (this process was performed on each of the four folds). Adaboost with leave one out validation was used as the machine-learning model. The 75% test sets had 91.6% specificity and 79% sensitivity across the four folds. The 25% validation sets had 89.7% specificity and 74.5% sensitivity across the four folds. The most consistent significant features (each feature being the connectivity between two regions) across the four folds largely supported previous findings implying a frontal-temporal-limbic hypothesis. We propose that resting state functional connectivity can be used in machine learning algorithms to help the correct diagnosis of BPD patients, avoiding misdiagnoses that are common and tremendously affect patients in several negative ways.

Disclosures: **S.N. Gosnell:** None. **R. Salas:** None. **K. Curtis:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.01/UU5

Topic: H.03. Schizophrenia

Support: NIMH

Title: Role of microRNA-936 in human neurons and adolescent mouse brains

Authors: *D. PANJA, Y. LI, Z. LI
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Abstract: MicroRNAs (miRs) are short, non-coding RNAs that alter gene expression by inhibiting transcription or promotes mRNA degradation. Individual miRNAs have many mRNA targets, and thus can act as master post-transcriptional regulators to contribute to the temporally and spatially complex gene expression patterns during brain development. miR-936 is a primate-specific miRNA expressed in the brain with unknown functions. We examined the expression pattern of miR-936 in human post-mortem brain tissues. To investigate the function of miR-936 in neurons, we expressed miR-936 in differentiating human neural stem cells and studied the phenotype of differentiated mature neurons. To study the function of miR-936 over-expression in behavior, we expressed miR-936 in the medial prefrontal cortex (mPFC) of mice via virus-mediated gene delivery and conducted various behavior tests. To search for the target genes

mediating the function of miR-936, we plan to validate the predicted target mRNAs of miR-936 using a fluorescence reporter assay. With these studies, we expect to identify the role of miR-936 in neural development in the central nervous system.

Disclosures: D. Panja: None. **Y. Li:** None. **Z. Li:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.02/UU6

Topic: H.03. Schizophrenia

Support: NIH R01MH094358 (RPS)

Title: JAK-STAT1 regulated gene expression and association with symptomatology in psychosis

Authors: *J. K. MELBOURNE, B. FEINER, C. ROSEN, R. P. SHARMA
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Abstract: Elevated levels of proinflammatory cytokines and systemic markers of inflammation are widely reported in individuals with psychotic disorders. We have demonstrated that a subset of individuals with a diagnosis of schizophrenia have elevated levels of activated STAT1 in peripheral blood mononuclear cells (PBMCs). JAK-STAT1 signaling regulates the expression of a wide range of immune effector genes and inflammatory cellular activity. While some general markers of peripheral inflammation have been associated with clinical characteristics and specific symptom domains, the association of STAT1 regulated genes with these measures has not been addressed in the scientific literature. PBMCs were isolated from blood samples collected from 63 participants with a diagnosis of schizophrenia, 23 participants with a diagnosis of bipolar disorder with psychosis and 44 controls. Quantitative real-time PCR was used to determine the mRNA expression of a panel of STAT1 regulated genes including C4A, STAT1, IRF-1 and CXCL10. At the time of the blood draw clinical characteristics such as illness duration and psychotropic medication usage were collected, along with symptom measures such as the Positive and Negative Syndrome Scale (PANSS) and the MATRICS Consensus Cognitive Battery. We found altered expression of some, but not all, STAT1 regulated genes in participants with psychosis compared to controls. Additionally, STAT1 regulated genes were associated with measures of symptomatology in participants with a psychiatric diagnosis. For example, C4A mRNA expression is positively correlated with the presence and severity of delusions across diagnostic groups. Further characterization of dysregulated immune cell signaling in psychosis is necessary to inform theory and the development of improved treatment options.

Disclosures: J.K. Melbourne: None. **B. Feiner:** None. **C. Rosen:** None. **R.P. Sharma:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

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Program#/Poster#: 173.03/UU7

Topic: H.03. Schizophrenia

Support: NIH MH108867

Title: Characterization of copper transporter CTR1 in normal postmortem hippocampus

Authors: *C. NGUYEN[1], K. E. SCHOONOVER[2], S. J. MABRY[2], C. B. FARMER[2], R. C. ROBERTS[2]
[1]Psychiatry, Univ. of Alabama At Birmingham, Birmingham, AL; [2]Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Copper is crucial for several cellular functions including proper monoamine metabolism, mitochondrial activity, and myelination. Abnormal copper levels are implicated in several brain disorders such as Menke's disease, Wilson's disease, and probably schizophrenia (SZ). In fact, experimental manipulations that decrease copper (such as feeding the copper chelator cuprizone) produce demyelination, dopamine increases, decreases in expression of oligodendrocytic proteins and SZ-like behavioral impairments. Copper transporter CTR1 transports copper across the blood brain barrier, but has rarely been studied in human postmortem brain. In this study we used immunohistochemistry to localize CTR1 in the medial temporal lobe of seven normal controls: 4F&3M; mean PMI and age were 7hr and 38yrs. Grey and white matter were analyzed separately for hippocampus and entorhinal cortex (ENT). Pyramidal neurons in stratum pyramidale (CA1 and CA3), subiculum and ENT were labeled along with proximal dendrites. The granule cell layer exhibited diffuse staining as well as some defined neuronal staining. CA4 contained labeled neurons and processes. Stratum moleculare, oriens and radiatum exhibited labeling in processes. Labeled glial cells were present around capillaries throughout all regions. White matter regions (fornix, alveus, and white matter in the subiculum and ENT) had labeled fibers, large puncta and some glial cells. At the electron microscope level, endothelial cells and astrocytes forming the blood brain barrier were stained. The large labeled punctate structures confined to the white matter were fibrous astrocytes. This study yields novel information about cell- and layer-specific CTR1 copper transport in postmortem human hippocampus, which could elucidate disease state etiology.

Disclosures: C. Nguyen: None. **K.E. Schoonover:** None. **S.J. Mabry:** None. **C.B. Farmer:** None. **R.C. Roberts:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

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Program#/Poster#: 173.04/UU8

Topic: H.03. Schizophrenia

Support: NIH MH108867

Title: Abnormalities in the copper transporters ATP7A and CTR1 in postmortem schizophrenia substantia nigra

Authors: *K. E. SCHOONOVER[1], R. C. ROBERTS[2]
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Abstract: Dysbindin is downregulated in several regions of the brain in schizophrenia. One of dysbindin's functions is to modulate copper (required for monoamine metabolism and myelination). The substantia nigra possesses one of the highest copper contents in the human brain. The current study used Western blot analysis to compare copper transporters ATP7A and CTR1, and dysbindin isoforms 1A, and 1B/C in postmortem substantia nigra in schizophrenia subjects (n=15) and matched controls (n=11); significant results are noted. The combined schizophrenia group exhibited decreased levels of CTR1 (42.6% decrease) and dysbindin isoform 1B/C (18.8% decrease) versus controls. When subdivided by medication status (medicated or unmedicated), the CTR1 decrease was similar in both groups versus controls, suggesting no medication effect. ATP7A levels were decreased in unmedicated versus medicated subjects (38.3% decrease) and controls (35.3% decrease), suggesting medication-induced rescue. When subdivided by treatment response, responders exhibited decreased CTR1 levels versus controls (47.1% decrease), while resistant subjects had decreased dysbindin 1B/C levels versus controls (32.1% decrease). A positive correlation between dysbindin 1B/C and CTR1 was observed in controls that was absent in schizophrenia subjects (p=0.029) and medicated subjects (p=0.03). A positive ATP7A/dysbindin 1A relationship was observed in unmedicated subjects that was absent in medicated subjects (p=0.007) and controls (p=0.003). Unmedicated subjects exhibited a negative relationship between dysbindin 1A and 1B/C that was lacking in medicated subjects (p=0.048). These results provide the first evidence of disrupted copper transport into and within nigral cells in schizophrenia, potentially related to isoform specific abnormalities of dysbindin and antipsychotic treatment.

Disclosures: K.E. Schoonover: None. **R.C. Roberts:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.05/UU9

Topic: H.03. Schizophrenia

Title: Catechol-o-methyltransferase SNPs rs4818 and rs4680 are associated with protein levels independent of psychiatric disorder

Authors: *G. PARKIN[1,2,3], M. UDAWELA[1,2,3], A. GIBBONS[1,3], B. DEAN[1,2,3]
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Abstract: Catechol-o-methyltransferase (COMT) is responsible for up to 60% of dopamine inactivation in the human dorsolateral prefrontal cortex (DLPFC) with a proposed link to cognitive function. SNP rs4680 in particular has been well-covered in academic literature in this regard. Our laboratory recently showed that levels of cortical muscarinic M1 receptor 1 (*CHRM1*) mRNA varied significantly depending upon genotype at *COMT* single nucleotide polymorphisms (SNPs) rs4818 and rs4680, but not rs737865 or rs165599. These data suggest COMT could affect cognition by influencing both the dopaminergic and cholinergic neurotransmitter systems in the CNS. To further investigate the impact of COMT on the dopaminergic system of the CNS we postulated that COMT genotypes known to affect the functionality of COMT would be associated with differing levels of cortical COMT protein. Therefore, as there are two different isoforms of COMT, one being membrane bound (MB) and located in non-dopaminergic neurons and the other being soluble (S) and located in glia, we measured levels of MB-COMT and S-COMT in the cortex (Brodmann's area 9) from 212 individuals, 126 of whom had psychiatric disorders. We show that levels of S-COMT, but not MB-COMT, varied with genotype at rs4818 and rs4680, but not rs737865 and rs165599 (protein levels at rs4818 genotype CC<GG, p=0.014, CG<GG, p=0.031; rs4680 genotype AA<GG, p=0.015), which reflects what was shown previously for *CHRM1* expression. Neither COMT genotype nor COMT protein levels varied with diagnosis (p>0.05). COMT protein levels did not correlate with age, sex, brain pH, post-mortem interval, duration of illness or suicide completion. Given rs4818 and rs4680, but not rs165599 and rs737865, are associated with cognitive functioning, our results suggest that S-COMT, but not MB- COMT, may play a specific role in CHRM1-mediated cognition and that this may be related to levels of S-COMT in glia.

Disclosures: **G. Parkin:** None. **M. Udawela:** None. **A. Gibbons:** None. **B. Dean:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.06/UU10

Topic: H.03. Schizophrenia

Title: Schizophrenia polygenic score associations with hippocampal activation and DOPA decarboxylase activity

Authors: *M. WINSTON[1], R. RASETTI[4], M. GREGORY[2], B. KOLACHANA[3], C. HEGARTY[5], A. IANNI[2], P. KOHN[2], J. H. CALLICOTT, III[6], V. S. MATTAY[7], D. R. WEINBERGER[7], D. P. EISENBERG[8], K. F. BERMAN[9]
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Abstract: Hippocampal (HIP) dysfunction has been consistently identified as a neural correlate of schizophrenia. The underlying mechanisms of HIP dysfunction are still unclear but recent evidence suggests that abnormal dopamine (DA) modulation of CA1 pyramidal cells may contribute. Our previous findings showed diminished HIP BOLD signal during implicit encoding of novel stimuli in patients with schizophrenia and their healthy siblings when compared to healthy volunteers, suggesting that HIP activation during encoding is an intermediate phenotype in schizophrenia, potentially linked to genetic risk for the illness. In the present study we hypothesized that healthy participants with higher schizophrenia genetic risk would show 1) lower HIP activation during implicit encoding; and 2) lower HIP DA synthesis capacity. Seventy-eight healthy volunteers underwent fMRI at 3T using an implicit encoding task known to engage the hippocampus, and HIP presynaptic DA synthesis capacity was separately measured with [^{18}F]-FDOPA PET. Using the results from the Psychiatric Genomics Consortium second mega-analyses (PGC-SCZ2), for each healthy participant we generated polygenic risk scores (PRSs) for schizophrenia, which measure the amount of cumulative genetic risk across the genome. After imputation of genetic data, multiple schizophrenia PRSs for each participant were calculated using the p-value thresholds ranging from $p<1$ (all LD-independent SNPS) to $p<1x10^{-8}$ (most restrictive) and weighted by the -log (odds ratio) from the PGC-SCZ2 results. Partial correlations tested for associations between PRSs and [^{18}F]-FDOPA PET K_i values. GLM (SPM8) tested for association between PRSs and voxel-wise BOLD activation across the hippocampus.
HIP [^{18}F]-FDOPA negatively correlated with the schizophrenia PRSs obtained from the most restrictive p values thresholds: PRSs p-threshold = 10^{-6}, r = -0.197, p= 0.090; PRSs p-threshold

$=10^{-7}$, r=-0.241, p= 0.038; PRSs p-threshold $=10^{-8}$, r = -0.28, p = 0.014. A negative correlation between bilateral HIP BOLD activation and PRSs was also observed at the 10^{-8} threshold (right hippocampus $p_{FWE\text{-}within\text{-}ROI} = 0.003$; left hippocampus $p_{FWE\text{-}within\text{-}ROI} =0.09$). No significant results were observed at the whole brain level or with PRSs at more liberal thresholds.
As initially hypothesized, healthy participants who displayed diminished hippocampal BOLD signal during encoding of neutral scenes, a known schizophrenia intermediate phenotype, were found to have higher PRSs for schizophrenia. Interestingly, this increased genetic risk was also correlated with diminished HIP dopamine synthesis capacity.

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Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.07/UU11

Topic: H.03. Schizophrenia

Title: The mechanism of nuclear localization of Gomafu, a schizophrenia-related long non-coding RNA

Authors: *G. UMEMOTO[1], S. NAKAGAWA[2], M. YOSHIDA[3], M. HATTORI[1], H. TSUIJI[1]
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Abstract: Gomafu is a long non-coding RNA (lncRNA) highly expressed in the central nervous system of higher vertebrates. In a cell, Gomafu constitutes a novel nuclear body, which overlaps with no known nuclear bodies. Gomafu associates with splicing factors such as SF1, SRSF1, and QKI and regulates alternative splicing of schizophrenia-related genes *DISC1* and *ERBB4*. Moreover, Gomafu knockout mice exhibit hyperactivity with enhanced responsiveness to psychostimulant methamphetamine. While Gomafu is a lncRNA that is spliced and polyadenylated, it is never transported to cytoplasm. The mechanism of nuclear localization of Gomafu is unknown.
In this study, we asked whether splicing inhibition impairs nuclear retention of Gomafu, because a splicing inhibitor Spliceostatin A (SSA) impairs the nuclear retention of some pre-mRNAs that is normally localized in nucleus to be spliced. HeLa cells expressing Gomafu were treated with SSA and the localization of Gomafu was analyzed by fluorescent *in situ* hybridization. We found that Gomafu was exported to cytoplasm by SSA treatment. Inhibition of splicing by SSA causes an enlargement of nuclear speckle. We asked which occurs first, the enlargement of nuclear

speckle or translocation of Gomafu. We found that Gomafu was exported to cytoplasm after the enlargement of nuclear speckle. Because the enlarged speckle contains unspliced pre-mRNA and splicing factors, these molecules may affect the retention of Gomafu.
Next, we asked whether inhibition of active spliceosome by antisense morpholino oligonucleotide (AMO) against U4 small nuclear RNA (snRNA), which is an essential component of spliceosome, affects localization of Gomafu. U4 AMO treatment caused enlargement of nuclear speckles, abnormal accumulation of polyadenylated pre-mRNA, and export of Gomafu to cytoplasm. Therefore, both inhibition of U2 small nuclear ribonucleoprotein (snRNP) function by SSA and inhibition of U4/U6 snRNPs formation by U4 AMO caused inhibition of nuclear retention of Gomafu. These results indicate that inhibition of mature spliceosome and/or abnormal accumulation of polyadenylated pre-mRNA cause abnormal transport of Gomafu to cytoplasm, and suggest that spliceosomal components are responsible for nuclear retention of Gomafu.

Disclosures: G. Umemoto: None. **S. Nakagawa:** None. **M. Yoshida:** None. **M. Hattori:** None. **H. Tsuiji:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.08/UU12

Topic: H.03. Schizophrenia

Support: RNA Bioscience Initiative Student Scholar

Title: Splicing of the PIK3CD gene in human brain and peripheral blood and expression alterations in schizophrenia

Authors: *V. L. FREGOSO[1,2], R. BERGER[3,2], A. J. LAW[4,2]
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Abstract: The *PIK3CD* gene encodes for the PI3K catalytic-subunit isoform, p110δ, a lipid kinase recently linked to several neurodevelopmental disorders. Our group has previously reported increased *PIK3CD* gene expression in patients with schizophrenia (SZ) and genetic association to risk variants in the gene. Recently it has emerged that regulation of the *PIK3CD* gene is more complex than previously appreciated, including the use of six alternative 5' untranslated leader exons (5'UTRs), alternative use of a splice junction creating a unique coding variant- P37, as well as identification of two anti-sense RNAs, AS1 and AS2. Since our original study used a 'pan-PIK3CD' assay, detecting all alternative transcripts, it is unknown whether specific alternative transcripts contribute to increased *PIK3CD* mRNA levels in SZ, or if

alterations in expression of AS1 or AS2 exist. Here, we comprehensively cloned, characterized and quantified alternative *PIK3CD* transcripts (through generation of custom-designed quantitative real-time PCR assays) in human brain and B-lymphoblastoid cell lines (LCLs). Firstly, in LCLs from an independent cohort of patients and controls (n=30 vs. 30) we identify increases in several *PIK3CD* transcripts in SZ. Transcripts encoding the two 5'UTRs, -2A and Alt1 ($F_{1,59}$=6.82, p=0.01; $F_{1,59}$=3.6, p=0.06); the functionally distinct splice variant, P37 ($F_{1,59}$=3.94,p=0.05) and AS1 and AS2 ($F_{1,58}$=14.04,p<0.001; $F_{1,58}$=5.71, p=0.02), were all significantly elevated in SZ. Given the association to SZ, we additionally mapped the tissue-specific and developmental expression of *PIK3CD* transcripts in the brain. *PIK3CD* transcript expression was mapped in normal adult (hippocampus and frontal cortex) and fetal human brain and compared to LCLs. We report for the first time that *PIK3CD* transcripts show tissue- and development-specific expression patterns, with several transcripts altered in SZ, including AS2, P37 and Alt1, preferentially expressed in the fetal brain. These findings implicate *PIK3CD* transcript-specific disruption in SZ and pave the way for examination of the genetic and/or molecular mechanisms underlying altered *PIK3CD* regulation in the disorder.

Disclosures: V.L. Fregoso: None. **R. Berger:** None. **A.J. Law:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

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Topic: H.03. Schizophrenia

Support: Neurocrine Biosciences, Inc.

Title: Effect of NBI-98782, a selective vesicular monoamine transporter 2 (VMAT2) inhibitor, on neurotransmitter efflux and phencyclidine- and amphetamine-induced locomotor activity: Relevance to tardive dyskinesia, antipsychotic behavior and cognition

Authors: *M. HUANG[1], *M. HUANG[1], W. HE[1], L. RAJAGOPAL[1], A. E. KUDWA[2], D. E. GRIGORIADIS[3], H. Y. MELTZER[1]
[1]Psychiatry and Behavior Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Neurocrine Biosci. Inc, San Diego, CA; [3]Neurocrine Biosci Inc, San Diego, CA

Abstract: Tardive dyskinesia (TD) is an involuntary movement disorder, resulting primarily from dorsal striatal (dSTR) dysfunction, genetic vulnerability and treatment with antipsychotic drugs (APDs). Valbenazine, a selective VMAT2 inhibitor and the precursor of NBI-98782, was recently approved as the first medication indicated for the treatment of TD in adults. Its efficacy may be due, in part, to inhibition of the release of vesicular neurotransmitters (NTs) including DA, norepinephrine (NE), 5-HT, acetylcholine (ACh), GABA and glutamate (Glu) which are

also critically important for cognition and psychosis. TD has been shown to diminish the ability of atypical APDs to improve cognitive function. Inhibition of VMAT2 would be expected to diminish the release of some, or all, of these NTs from presynaptic neurons. Our aim was to determine the effect of NBI-98782 and tetrabenazine on NT efflux from medial prefrontal cortex (mPFC) and dSTR using microdialysis in awake, freely moving mice, to characterize the interaction of NBI-98782 with APDs, and to assess whether NBI-98782 can attenuate locomotor increases observed in phencyclidine (PCP)- and amphetamine (AMP)-induced mouse models of psychosis. NBI-98782 and tetrabenazine (10 mg/kg, PO) decreased the efflux of DA, 5-HT, and NE, while increasing the efflux of DA metabolites DOPAC and HVA and the 5-HT metabolite 5-HIAA without changing ACh, Glu or GABA efflux in mPFC, dSTR, hippocampus, and nucleus accumbens which are regions of interest for cognitive-, psychotic-, and rewarded behaviors. Sub-chronic (sc) NBI-98782 (7 days, 10 mg/kg per day, PO) decreased basal DA and 5-HT efflux in both mPFC and dSTR. Acute NBI-98782 (10 mg/kg, PO) had similar effects on NT efflux in scNBI-98782-treated mice. NBI-98782 (10 mg/kg, PO) suppressed the atypical APDs, clozapine (10 mg/kg, ip) and olanzapine (3 mg/kg, ip)-induced DA efflux in both mPFC and dSTR, and ACh efflux in mPFC. NBI-98782 suppressed haloperidol (0.5 mg/kg, ip)-induced DA efflux in dSTR, but had minimal effect on GABA efflux, despite the fact that VMAT2 is involved in GABA transport. These results suggest decreased release of dSTR DA may contribute to its beneficial effects on TD. NBI-98782 (10 mg/kg, PO) attenuated PCP (10 mg/kg, ip)-induced DA, 5-HT, NE and Glu efflux, and AMP (2.5 mg/kg, ip)-induced DA and NE efflux, in both mPFC and dSTR, and PCP- and AMP-induced hyperlocomotion. These results suggest NBI-98782 may have actions similar to those of atypical APDs; further study is needed to determine its effects on cognition and psychosis.

Disclosures: **M. Huang:** None. **W. He:** None. **L. Rajagopal:** None. **A.E. Kudwa:** A. Employment/Salary (full or part-time):; employee. **D.E. Grigoriadis:** A. Employment/Salary (full or part-time):; employee. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

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Program#/Poster#: 173.10/UU14

Topic: H.03. Schizophrenia

Support: NIH Grant MH57440

CNPq/Brazil fellowship 200606/2015-8

Title: Alpha7 nicotinic receptor agonists reverse the hyperdopaminergic tone in the MAM model of schizophrenia

Authors: *G. A. NEVES, A. A. GRACE
Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Cholinergic neurotransmission has been implicated in the pathophysiology of neuropsychiatric disorders. Several post-mortem, genetic and epidemiologic studies link specifically the alpha7 nicotinic receptor subtype to schizophrenia, and the potential use of alpha7 modulators as a treatment strategy for this disturbance is an active field of research. However, studies to date have been limited to normal systems rather than on a validated neurodevelopmental model of schizophrenia. Moreover, knowledge about the differential impact of orthosteric and allosteric modulators in vivo is lacking. Thus, we are investigating the effects of alpha7 modulation on dopamine (DA) neuron activity in the ventral tegmental area (VTA) in the methylazoxymethanol acetate (MAM) animal model of schizophrenia. All experimental procedures were conducted according to NIH guidelines and were approved by University of Pittsburgh Institutional Animal Care and Use Committee. Sprague-Dawley pregnant dams were treated with MAM or saline on gestational day 17. Recordings of VTA dopamine neuron activity was performed on the male offspring at adulthood. The effects of four different drugs were evaluated: PNU282987 (full agonist), SSR180711 (partial agonist) NS1738 (type I positive allosteric modulator - PAM) and PNU120596 (PAM type II). Intravenous administration of alpha7 selective ligands did not induce a major change in the firing profile of spontaneously active DA neurons when dosed during cell recording. However, the type II PAM PNU120596 induced an increase in the number of active DA cells found in the VTA in the normal rats and an increase in their mean firing rate. In contrast, the full agonist PNU282987 and the partial agonist SSR180711 reduced the hyperdopaminergic tone in the MAM model of schizophrenia. Moreover, the partial agonist was also able to reduce DA neuron mean firing rate in the MAM rats. When SSR1800711 was infused into the ventral hippocampus (vHipp), opposite effects were also detected: an increase in the number of active DA cells in the control animals and a decrease in the MAM model. In summary, our results show that activation of alpha7 receptors can modulate VTA DA neuron population activity and these effects appear to be mediated at least in part by actions in the vHipp. Differences in the effects of the drugs between MAM and control rats point to an altered cholinergic tone in the MAM model consistent with observations in schizophrenia patients. Our data point to a direct receptor activation rather than an allosteric potentiation as the most promising molecular mechanism for developing new alternative or add-on therapy for schizophrenia.

Disclosures: **G.A. Neves:** None. **A.A. Grace:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

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Topic: H.03. Schizophrenia

Support: FUI Coinside

Title: The preclinical use of EEG evoked responses for drug discovery in brain disorders

Authors: *V. DUVEAU[1], B. POUYATOS[2], C. TOULLER[3], R. MAURY[3], C. DUMONT[3], C. ROUCARD[4], Y. ROCHE[2]
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Abstract: EEG and related methodologies have emerged as powerful tools in both clinical and preclinical research programs for the identification of physiological and pathological biomarkers. Nowadays EEG endpoints are largely used in the clinic to identify and evaluate a pathological state and/or as surrogate biomarkers for clinical trials (Alzheimer's disease, schizophrenia, autism, epilepsy…). EEG biomarkers are easily translatable from human to rodent offering a unique opportunity to develop more efficient drug discovery programs. In rodents, EEG responses evoked by auditory stimulation can be recorded in various brain areas and underlie the integration and processing of sensory information which are altered in a large number of neurological and psychiatric disorders. We can distinguish two main types of auditory evoked responses, the auditory evoked related potentials (AERP) and the auditory steady state response (ASSR). AERPs are composed of successive positive and negative deflections, which differ from their latencies and amplitudes and are well conserved throughout the evolution. ASSRs consist in cortical electrophysiological oscillations entrained to the frequency and phase of a periodic auditory stimulus presented at a rhythm in the gamma range (that is, 30-80Hz). ASSRs are believed to reflect the interplay between cortical pyramidal neurons and parvalbuminergic interneurons. Consistent with the theory of imbalance between cortical excitation and inhibition in schizophrenia, patients show reduced power and phase locking, to stimulations presented at 40Hz. In this work, we investigated the effect of pharmacologically induced models of Alzheimer's disease and schizophrenia on AERP and ASSR in mice. we identified functional biomarkers in mouse models of neuropsychiatric disorders using EEG and related methodologies. These specific biomarkers could represent a crucial tool for the identification, selection and validation of new innovative therapeutics.

Disclosures: V. Duveau: A. Employment/Salary (full or part-time):; SynapCell SAS. **B. Pouyatos:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Touller:** A. Employment/Salary (full or part-time):; SynapCell SAS. **R. Maury:** A. Employment/Salary (full

or part-time):; SynapCell SAS. **C. Dumont:** A. Employment/Salary (full or part-time):; SynapCell SAS. **C. Roucard:** A. Employment/Salary (full or part-time):; SynapCell SAS. **Y. Roche:** A. Employment/Salary (full or part-time):; SynapCell SAS.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.12/UU16

Topic: H.03. Schizophrenia

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Title: Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry

Authors: *L. G. NUCIFORA[1], T. TANAKA[1], L. N. HAYES[1], M. KIM[1], B. J. LEE[1], T. MATSUDO[2], F. C. NUCIFORA, Jr.[1], T. SEDLAK[1], R. MOJTABAI[2], W. EATON[2], A. SAWA[1]
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Abstract: The establishment of mechanism-driven peripheral markers is important for translational psychiatry. Many groups, including ours, have addressed molecular alterations in peripheral tissues in association with symptomatic changes in major illnesses. Oxidative stress is implicated in the pathophysiology of schizophrenia (SZ) and bipolar disorder (BP) through studies of patient peripheral tissues and animal models. Although the relationship between peripheral changes and brain pathology remain elusive, oxidative stress may bridge such translational efforts. Nonetheless, the molecular substrates of oxidative stress are not well defined in mental conditions. Glutathione (GSH) is a non-enzymatic antioxidant that eliminates free radicals, and has been suggested to play a role in SZ. We performed a cross-sectional study of 48 healthy controls, 52 SZ patients, and 62 BP patients to compare the levels of peripheral GSH by a biochemical enzyme assay. We show a significant reduction of plasma GSH in both

SZ and BP patients compared to controls. We evaluated possible influences of clinical characteristics on the level of GSH in SZ and BP. A decrease in GSH level correlated with PANSS total and positive scores for SZ and correlated with the PANSS general for BP. Taken together, we provide evidence that SZ and BP display a common molecular signature in the reduction of peripheral GSH in the psychosis dimension.

Disclosures: L.G. Nucifora: None. **T. Tanaka:** None. **L.N. Hayes:** None. **M. Kim:** None. **B.J. Lee:** None. **T. Matsudo:** None. **F.C. Nucifora:** None. **T. Sedlak:** None. **R. Mojtabai:** None. **W. Eaton:** None. **A. Sawa:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.13/UU17

Topic: H.03. Schizophrenia

Title: Treatment augmentation in schizophrenia and schizoaffective disorder

Authors: *H. C. RUDOLPH[1], J. L. LARIMORE[2]
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Abstract: Schizophrenia (SZ) and schizoaffective disorder (SzAD) are chronic neuropsychiatric disorders, often characterized by the combination of positive (e.g. hallucinations, delusions, thought disorders) and negative symptoms (e.g. affective flattening, apathy, social withdrawal). The most common method of treatment for these disorders is antipsychotic monotherapy. Currently, treatment augmentation in antipsychotic therapy for SZ and SzAD is one of the strongest options for patients with treatment-resistant illnesses or insufficient relief from antipsychotic monotherapy. This study examines the success of eight augmentation strategies that have emerged in existing literature as promising adjunctive treatments to provide optimal symptom relief with minimal side effects for patients with SZ and SzAD.

Disclosures: H.C. Rudolph: None. **J.L. Larimore:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

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Program#/Poster#: 173.14/UU18

Topic: H.03. Schizophrenia

Support: CNPQ

FAPERJ

Title: Auditory oddball training improves prepulse inhibition in serine racemase (-/-) mice

Authors: *G. D. GUERCIO[1], J. TRAVASSOS[2], S. COSTA[2], A. PEROZZO[2], L. MORORO[2], L. GENARO[2], L. SCORIELS[2], E. DE VILLERS-SIDANI[3], R. A. PANIZZUTTI[4]
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Abstract: The use of computer-based cognitive training for patients in order to ameliorate cognitive deficits in schizophrenia has increased in recent years. However, as this has been a highly heterogeneous approach, the results have been mixed, and the neurological underpinnings of these trainings remain largely unknown. To study the effect of an auditory oddball training in an animal model of schizophrenia, we used serine racemase (SR) -/- mice, which lack the conversion of L-serine to D-serine. These mice are known to have prepulse inhibition (PPI) deficits, a measure of a pre-attentive filtering mechanism that is also deficient in schizophrenia and may potentially contribute to cognitive deficits. Our goal was to test whether training SR -/- mice in an adaptive oddball task could treat PPI deficits. First, we replicated the finding that SR -/- mice have lower PPI (main effect genotype $p < 0.05$). Mice were then divided in training and sham groups. We observed that SR -/- performed worse in the oddball task, reaching lower levels throughout training (main effect $p < 0.01$). Interestingly, training didn't change PPI in SRR +/+ mice (t test $p > 0.05$) but improved PPI in SR -/- (t test $p < 0.05$). D-serine (i.p.) added to training increased the performance of SR -/- mice in the oddball task (main effect $p <0.01$). Our results show for the first time that a cognitive training strategy can improve PPI in an animal model of schizophrenia. We will now determine whether the addition of D-serine to cognitive training has a synergistic effect on PPI, and whether these findings translate to patients with schizophrenia.

Disclosures: G.D. Guercio: None. **J. Travassos:** None. **S. Costa:** None. **A. Perozzo:** None. **L. Mororo:** None. **L. Genaro:** None. **L. Scoriels:** None. **E. de Villers-Sidani:** None. **R.A. Panizzutti:** None.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 173.15/UU19

Topic: B.04. Ion Channels

Title: Dissecting the neurophysiological role of $Ca_V3.3$ in thalamic reticular nucleus: Translating emerging genetics into potential novel therapeutic approach for schizophrenia

Authors: *A. GHOSHAL[1], L. YANG[1], V. G. LOPEZ-HUERTA[1], M. A. ARIAS-GARCIA[1], D. BAEZ-NIETO[1], A. ALLEN[1], D. S. UYGUN[2], R. E. STRECKER[3], R. W. MCCARLEY[4], S. PURCELL[5], Q. ZHANG[6], X. MAO[7], T. NICHOLSON[7], Z. FU[1], G. FENG[6], E. M. SCOLNICK[1], J. Q. PAN[1]

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Abstract: Genetic analyses of large patient cohorts have identified CACNA1I that encodes for the T-type voltage gated calcium channel $Ca_V3.3$, as a gene associated with schizophrenia risk. $Ca_V3.3$ is the primary T-type Ca^{2+} channel expressed in the GABAergic neurons of the thalamic reticular nucleus (TRN). It has been hypothesized that $Ca_V3.3$ dependent oscillatory properties of TRN neurons are essential for sleep spindle generation, which is impaired in some schizophrenia patients. Recently, a *de novo* missense variation R1346H of $Ca_V3.3$ was identified in individuals with schizophrenia. Our group have previously demonstrated that R1346H is associated with lower $Ca_V3.3$ protein levels, reduced glycosylation, lower membrane surface levels of $Ca_V3.3$ and reduced Ca^{2+} current density when expressed in human cell lines compared to wild-type. However, the impact of this mutation on the physiological properties in neurons majorly expressing $Ca_V3.3$ (TRN neurons) and *in vivo* is yet to be known. In this study, using CRISPR-Cas9 technique we generated mice carrying this mutation (RH) as well as a knock-out mice completely lacking $Ca_V3.3$ (KO) and employed slice electrophysiology to characterize changes in TRN physiology. Brain slices containing the TRN were prepared from male P21-P30 mice and T-type Ca^{2+} currents ($[Ca]_T$), intrinsic membrane properties as well as depolarization induced tonic firing and hyperpolarization induced rebound burst firing were recorded and compared across wild-type (WT), KO and RH mice. $[Ca]_T$ were prevalent in the TRN neurons of WT mice but were dramatically reduced in the KO mice, validating the fact that $Ca_V3.3$ acts as the primary $[Ca]_T$ source in these neurons. Consistent with our previous observation in HEK293 cells, $[Ca]_T$ density was significantly reduced in the TRN neurons of RH mice. We next observed that unlike the WT mice, TRN neurons of KO mice rarely showed hyperpolarization induced oscillatory rebound burst firing, corroborating previous findings that this property is $Ca_V3.3$ dependent. Interestingly, rebound burst firing was present in the TRN neurons of RH mice but there was significant reduction in its number and efficiency as compared to their WT littermates. Depolarization induced tonic firing, resting membrane potential and input resistances were all unaffected in both the RH and KO mice. We are currently performing *in vivo* EEG experiments to identify a possible role of $Ca_V3.3$ and TRN rebound bursting in sleep spindle generation. Taken together these results provide the first set of evidence towards validating $Ca_V3.3$ as a novel therapeutic target for schizophrenia.

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Poster

173. Schizophrenia: Pathophysiology and Therapeutics

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH grant AA022448

Title: Modulation of dopamine receptors significantly impacts ivermectin-mediated effects on DARPP-32/ERK/CREB phosphorylation in the ventral striatum of C57BL/6J mice

Authors: *S. KHOJA[1], L. ASATRYAN[2], M. W. JAKOWEC[3], D. L. DAVIES[4]
[2]Titus Family Dept. of Clin. Pharm., [3]Neurol., [4]Titus Family Dept of Clin. Pharm., [1]USC, Los Angeles, CA

Abstract: Ivermectin (IVM) is a semi-synthetic dihydro lactone derivative of avermectins, which is derived from soil actinomycete, *Streptomyces avermitilis*. We previously demonstrated IVM to be a positive modulator of purinergic P2X4 receptors (P2X4Rs). P2X4Rs are cation permeable ion channels activated by adenosine-5'-triphosphate (ATP). We reported that IVM could regulate phosphorylation of certain signaling molecules in the striatum, including dopamine and cyclic-AMP regulated phosphoprotein of 32kDa (DARPP-32), extracellular-regulated kinase 1/2 (ERK 1/2) and cyclic-AMP response element binding protein (CREB), providing insights into mechanism of action of IVM. Notably, IVM's effects are characteristic of pharmacology of drugs acting on dopamine (DA) receptors. For example, IVM-mediated enhancement of DARPP-32 and ERK 1/2 phosphorylation in the dorsal striatum is strikingly reminiscent of DA receptor agonist activity. This led us to hypothesize that IVM's signaling cascade may, in part, be DA receptor-dependent. This hypothesis is further supported by previous observations wherein IVM's behavioral effects on sensorimotor gating and motor activity can be modulated by dopaminergic drugs. In the present study, we continued to investigate the interaction between IVM and dopaminergic drugs on signaling pathways. This was accomplished by testing the effects of antagonists, SCH 23390 (1mg/kg) for DA D1 receptor and raclopride (3 mg/kg) for DA D2 receptor on IVM (10 mg/kg) -induced phosphorylation of DARPP-32, ERK 1/2 and CREB in the ventral striatum and prefrontal cortex (PFC) of male C57BL/6J mice. We also tested the interaction between IVM (5mg/kg) and D1 receptor agonist, SKF 82958 (0.1mg/kg) in regulation of these phosphoproteins in the same brain regions. IVM (10mg/kg) significantly increased DARPP-32, ERK 1/2 phosphorylation and tended to have similar effects on CREB phosphorylation in the ventral striatum, but not in the PFC. SCH 23390 and raclopride significantly blocked IVM-mediated increase in DARPP-32 phosphorylation in

the ventral striatum. Raclopride, but not SCH 23390, blocked IVM-mediated increase in ERK 1/2 phosphorylation in the ventral striatum. SKF 82958 significantly increased DARPP-32 phosphorylation in the presence of IVM in the ventral striatum. Neither of these drugs had any effect on IVM-induced CREB phosphorylation in the ventral striatum and PFC. Overall, these findings suggest an involvement for DA receptors in IVM-mediated signaling cascades in the ventral striatum, indicating a complex interaction between P2X4Rs and DA receptors on signaling pathways that are critical for various behavioral functions.

Disclosures: S. Khoja: None. **L. Asatryan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on a patent for the use of ivermectin for treatment of alcohol use disorder. **M.W. Jakowec:** None. **D.L. Davies:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Daryl Davies is inventor on a patent for use of ivermectin for treatment of alcohol use disorder.

Poster

173. Schizophrenia: Pathophysiology and Therapeutics

Location: Halls A-C

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Program#/Poster#: 173.17/UU21

Topic: H.03. Schizophrenia

Support: NIH

Title: Nuclear GAPDH cascade and autofluorescence: A possible mechanism-guided high throughput biomarker for cognitive flexibility in severe psychiatric illnesses

Authors: F. E. DOMINGUEZ[1], A. RAMOS[1], N. J. ELKINS[1], T. TSUJIMURA[1], C.-Y. LIN[1], *M. NIWA[2], K. ISHIZUKA[1], A. SAWA[1]
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Abstract: Establishing biomarkers for severe psychiatric illnesses such as schizophrenia (SZ) is crucial in early diagnosis and intervention before symptoms exacerbate. Moreover, if biomarkers are based in the pathophysiological mechanism of the disease, they can be used to screen potential therapeutic compounds.
Our study found augmented cellular autofluorescence in lymphoblasts (LB) of SZ patients as compared to matched controls. Levels of AF were inversely correlated to cognitive flexibility, an important domain of executive functioning. In hopes that the measurement of autofluorescence can be developed as a high throughput biomarker, we tested whether such observations from LB were also seen in fresh peripheral blood mononuclear cells (PBMC). In a pilot study, we detected intrinsic autofluorescence signal from PBMC on a microplate reader.

Next, we addressed a mechanism by which autofluorescence is augmented in SZ pathology. The level of autofluorescence was correlated with the presence of reactive oxygen species, indicating an underlying mechanism associated with oxidative-stress for this unique cellular phenotype. Previously, our group has reported that a small fraction of the glycolytic enzyme Glyceraldehyde-3-phosphate Dehydrogenase (GAPDH) undergoes post-translational modification and nuclear translocation in order to mediate stress signaling as a transcription factor (i.e. the "nuclear GAPDH cascade"). We developed a novel compound, "RR," that blocks nuclear translocation of GAPDH. Interestingly, "RR" attenuated augmentation of AF in human LB, indicating that the nuclear GAPDH cascade contributes to the augmented cellular autofluorescence in SZ.
In summary, we propose cellular autofluorescence as a possible mechanism-guided high throughput biomarker for severe psychiatric illnesses, which is desperately needed. Note, we have explored the link between this cellular mechanism (the nuclear GAPDH cascade) and SZ-associated behavioral changes in lipopolysaccharide (LPS)-treated mouse model (see a presentation by Ramos et al in this meeting).

Disclosures: **F.E. Dominguez:** None. **A. Ramos:** None. **N.J. Elkins:** None. **T. Tsujimura:** None. **C. Lin:** None. **M. Niwa:** None. **K. Ishizuka:** None. **A. Sawa:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.01/UU22

Topic: I.02. Systems Biology and Bioinformatics

Support: FAPESP 2013/20378-8

Title: Comparative analysis of proteic profile in the dorsal hippocampal formation of rats submitted to suppression of the licking response

Authors: *R. B. GAIARDO[1], A. P. PEDROSO[2], A. K. TASHIMA[2], M. M. TELLES[1], S. M. CERUTTI[1]
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Abstract: Dorsal hippocampal formation (dHF) of rats has often been related to the context-conditioned fear memory formation. However, recent studies from our group suggest the involvement of dHF in the acquisition of the conditioned the licking response. This study assessed the differential protein profile in the dHF of adult male Wistar rats submitted to lick suppression. The behavioral procedure was conducted for eight or forty days. For five consecutive days, the rats were submitted to acquisition of licking response (baseline). On day 6, the animals were submitted to four tone-shock (CS-US) pairings (fear conditioning). On the 7th

(CS-US 2 group) or 39th day (CS-US 40 group), the animals were subjected to reacquisition of the licking response sessions, as performed during the acquisition of the licking response to re-establish drinking behavior after conditioning and to reduce contextual cues. On 8th or 40th day after conditioning, rats were tested for retention of the fear memory, which evaluated the suppression of licking response calculated to the CS on ten consecutive trials. The time to complete ten licks pre-tone (A) and during tone (B) was used to calculate the suppression ratio (SR) as the ratio of B/(A+B). Twenty-four hours after completion of the behavioral experiments the animals were decapitated and samples of the dHF were removed for shotgun proteomics in a Synapt G2 HDMS q-TOF mass spectrometer coupled to a nanoAcquity UPLC chromatographic system. The naïve group was used as control of protein expression. Analysis of SR showed that CS-US 2 (SR_1=0.73) and CS-US 40 (SR_1=0.82) groups had the acquisition of conditioned suppression, which was verified by the suppression ration in the first trial of retention test. Our results revealed differential expression of 1,395 proteins in the dHF. After application of the exclusion criteria, 265 proteins were compared between the groups, which 29 had significant differential expression ($P<0.05$). It is interesting to point out that among the altered proteins, they include different functional groups as downstream signaling pathways to serotonin receptor subtypes 5-HT1R, 5-HT2R, 5-HT3R and 5-HT4R; alpha and beta (subtypes β1, β2 and β3) adrenergic receptor; dopamine receptor; ionotropic glutamate receptors (NMDAR and AMPAR); metabotropic glutamate receptor groups II and III; nicotinic and muscarinic (subtypes M1, M2, M3 and M4) cholinergic receptors as well as proteins involved in synaptic vesicle trafficking and adrenaline and noradrenaline biosynthesis. Our results can provide further evidence for the dHF involvement in the acquisition of the conditioned emotional response.

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Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.02/UU23

Topic: I.02. Systems Biology and Bioinformatics

Support: NIH grant OD011190

Title: Building mouse models: A resource for mutant mouse lines expressing Cre-recombinase using the CrePortal www.creportal.org

Authors: *H. ONDA[1], L. BECHTEL[2], S. A. MURRAY[2], C. L. SMITH[1]
[1]Mouse Genome Informatics, [2]Genet. Resource Sci., The Jackson Lab., Bar Harbor, ME

Abstract: Mutant mice with spatially and temporally specific expression of recombinase have proven to be invaluable tools for many labs to study cell type and stage specific gene interactions during normal brain development or neurological disease processes. Those mutant mouse lines include all recombinase variations, notably Cre, but also Flp, Dre, phiC31, and various inducible forms of these recombinases. The technique called conditional mutagenesis utilizes mice carrying a target gene with inserted loxP or other target sites which are mated with mice bearing Cre-recombinase transgenes or knock-in alleles. In planning experiments, many research labs often spend large amounts of time and resources to determine or confirm when and where Cre-recombinase is expressed. To help researchers build appropriate mouse models, the CrePortal (www.creportal.org) facilitates identification of the most suitable Cre mouse lines for such conditional mutagenesis experiments by providing a centralized, comprehensive set of well-annotated Cre-driver mouse lines from both published and unpublished sources. The information includes data generated from a high-throughput pipeline characterizing excision activity in a wide range of tissues at multiple time points for available Cre-driver lines. Many Cre recombinases are expressed in previously unreported tissues or cells beyond the intended tissues or cell types; thus providing those data to the scientific community will help the interpretation of phenotype(s) for these mouse models. The database is searchable by anatomical system in which Cre is assayed and/or by a specific driver to find a relevant allele with links to detailed information for the Cre recombinase line. The search result also displays the following: a list of drivers, allele symbols, associated gene and allele name, a list of tissues in which recombinase activity was detected or not detected, the inducible agent (if required), links to the International Mouse Strain Resource (IMSR, www.findmice.org) for locating those strains available through public repositories, links to references utilizing the line, and allele synonym(s). Display pages are hyperlinked to Mouse Genome Informatics resources (www.informatics.jax.org) for retrieval of phenotype information associated with conditional genotypes, and to further provide more detailed Cre activity summary and phenotypic information for genotypes involving the Cre transgene or allele. We encourage you to explore the CrePortal and submit your laboratory’s Cre line additional observations for inclusion at www.informatics.jax.org/submit.shtml.

Disclosures: H. Onda: None. **L. Bechtel:** None. **S.A. Murray:** None. **C.L. Smith:** None.

Poster

174. Systems Biology and Bioinformatics

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Program#/Poster#: 174.03/UU24

Topic: I.02. Systems Biology and Bioinformatics

Title: Artificial intelligence and multi-omic assessment of plasma reveals molecular signature of parkinsons disease

Authors: M. A. KIEBISH[1], P. NARAIN[1], B. SCHUELE[2], S. AKMAEV[1], V. VEMULAPALLI[1], J. GARREN[1], V. TOLSTIKOV[1], F. GAO[1], K. PANAGOPOULOS[1], E. CHEN[1], L. REES[2], F. KAUSAR[2], P. TEKUMALLA[1], L. RODRIGUES[1], V. VISHNUDAS[1], S. GESTA[1], C.-L. BARLOW[2], N. NARAIN[1], *R. SARANGARAJAN[1], J. LANGSTON[2]
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Abstract: Parkinsons Disease is a progressive neurodegenerative disorder in which loss of dopaminergic neurons in the substatia nigra results in a stratified clinical presentation in controlled movement in patients. Only 3-5% of Parkinsons patients result from a genetic abnormality and the vast majority of treatment regiments focus on treating the symptomatic aspect of the disease rather than tiered through molecular stratification or staging. Additionally, there is significant clinical benefit to treat Parkinsons Disease at the earliest stage as well as identify at risk populations from a molecular level. Here in, we prospectively collected and analyzed plasma from 196 Parkinsons Disease patients as well as 196 age matched non-diseased controls. Close to 1000 clinical features were collected on each patient. We employed proteomics, signaling and structural lipidomics as well as metabolomics platforms to identify plasma biomarkers and evaluate their utility for diagnosis and clinical association with Parkinsons Disease. The unbiased global profiling and integration of the data and clinical-pathologic features have led to the identification of molecular fingerprints differentiating Parkinsons Disease patients from non-diseased controls. This was accomplished using a Bayesian Artificial intelligence analysis to identify cause and effect relationships among molecular and clinical features along with conventional diagnostic assessment. Integrated AI and OMIC analysis demonstrated that 2 metabolites, 1 signaling lipid, 3 proteins, and 3 structural lipids demonstrating potential diagnostic utility for stratification of non-disease controls compared to Parkinsons Disease patients. Additionally, the 2 metabolites identified demonstrated preliminary utility in stratification of PD staging using Hoehn and Yahr classification. Further, the diagnostic analytes did not seem affected by concomitant medication. Incorporation of informative non-classical diagnostic criteria of Parkinsons Disease also increased the overall diagnostic utility of clinical and molecular integration. Here in, we demonstrated that an unbiased data driven approach utilizing multi-omic analysis and AI integration was able to identify informative markers to stratify Parkinson Disease in a prospective cohort.

Disclosures: The Disclosure Block has exceeded its maximum limit. Please call Tech support at (217) 398-1792 for more information.

Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: NSF

Title: Unexpected complexities of numerically simpler neural systems as revealed by novel single-cell "omics" technologies

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Abstract: *Aplysia californica* is one of the most effective model organisms for studying the cell biology of neurons, determining how different patterns of interconnections control behaviors, and elucidating the nature of modifications in the pattern of interconnections produced by learning and memory. This is also an ideal experimental model for bringing 'omic' sciences to all levels of neuronal organization, starting from the defined subcellular domain in a single neuron to the neural circuits underlying complex stereotyped or learned behaviors. Therefore, we now integrate the innovative single-cell technologies such as single-cell methylomics, RNA-seq, epitranscriptome, including direct single-cell analyses of RNA modifications, to investigate gene regulation within the very same identified neurons both in controlled and chemical learning-induced conditions. We characterized the dynamic operation of *Aplysia* genome within multiple identified neurons in circuits controlling feeding and defensive behaviors using scRNA-seq and scMethyl-seq with >20,000 overall transcriptome and 600 x methylome coverage. *Aplysia* shares with humans >80% of genes controlling signal transduction, epigenetic machinery and genes associated with neurological disorders. However, with 8,000-14,000 genes expressed in each tested neuronal type, we find that morphologically and electrophysiologically similar sensory neurons are the most genetically heterogeneous neuronal population, compared with sequenced motor- and interneurons. In part, these differences are due to cell-specific histone variants and chromatin remodelers. Moreover, canonical pan-neuronal markers such as transcription factors or RNA-binding proteins like ELAV are not the best indicators of neurons, but unique signaling peptides and noncoding RNAs show the most district cell specificity. Hierarchical and unbiased molecular classification of neurons at the single-cell scale (using scRNA-seq, single-cell-methylome assays, and epitranscriptomics) does not correlate with neuronal morphology and functional position in the circuits. In contrast, RNA-modifications are good indicators of both cellular individuality and plasticity. The unbiased integration of multiple multi-omics approaches reveal remarkable, and hidden, cell specificity (validated by *in situ* hybridization) as well as an extensive degree of molecular complexity and apparent redundancy controlling neural identity that exceed any level described so far.

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Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.05/UU26

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Grant 1516527

Title: Making structured neurophysiology data searchable using Semantic Web methods

Authors: *J. L. TEETERS, P. JEŽEK, S. MACKESEY, F. SOMMER
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Abstract: The representation of neuroscience data that enables searching and sharing between labs is challenging. Custom data structures specific to a lab need to be represented in a standardized way so that common tools can be deployed. Semantic Web technologies offer potential for representing a variety of neuroscientific data in a common format. The primary unit of data in the Semantic Web is the RDF (Resource Description Framework) triple; data represented in RDF triples is searchable with a query language called SPARQL. We present a system for mapping neuroscience metadata in two existing formats into RDF triples:
1) DataCite [1], provides an infrastructure to register structured metadata describing shared datasets and is used to generate a DOI that can be used to cite datasets. Registration of a dataset requires submitting an XML document with metadata describing the dataset. Since DataCite is designed to work with data from any domain, it does not include predefined structures that are specific for neurophysiology metadata.
2) The Neurodata Without Borders: Neurophysiology (NWB) format [2,3] provides standard ways of storing neurophysiology data of different types and associated metadata. The NWB format can be extended in a structured way by defining extensions using a specification language or through custom additions that are not defined using an extension.
The data used to develop these methods is available at CRCNS.org, an online repository hosting publicly available neurophysiology data.
[1] http://datacite.org
[2] http://nwb.org/nwb-neurophysiology/
[3] http://dx.doi.org/10.1016/j.neuron.2015.10.025

Disclosures: **J.L. Teeters:** None. **P. Ježek:** None. **S. Mackesey:** None. **F. Sommer:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.06/UU27

Topic: I.02. Systems Biology and Bioinformatics

Title: The renderer: A toolkit for managing and materializing large scale image volumes

Authors: *E. T. TRAUTMAN, T. DOLAFI, E. PERLMAN, S. SAALFELD
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Abstract: Large scale imaging projects commonly produce millions of image files and associated meta-data. This information needs to be managed and organized, images registered and aligned to each other, and resulting image volumes visualized, inspected and navigated. Typically, an ecosystem of software tools is developed to analyze such datasets. These tools, ideally, should be backed by a flexible common service software infrastructure that keeps track of image meta-data and transformations while providing varied materialized (rendered) views of the images and arbitrary sub-volumes. To this end, we have developed the Renderer toolkit. The Renderer provides RESTful HTTP APIs to manage a persistent data model that describes image transformations, channels and other meta data. The HTTP API ensures that the data model can be accessed by software written in almost any language. The Renderer utilizes the mpicbg transformation library (Fiji/ImageJ) to support a rich set of linear and non-linear transformations that can be chained together in arbitrary sequences. The toolkit's multi-tier architecture allows for independent scaling of database, web service, and client-side rendering components enabling parallelized large scale reconstruction processing. We have developed Java stand-alone clients as well as Spark framework clients to support the most common distributed tasks, including bulk stack rendering and coordinate mapping between different alignments. The Renderer is experiencing a growing user-base. It is available as Open Source on GitHub.

Disclosures: E.T. Trautman: None. **T. Dolafi:** None. **E. Perlman:** None. **S. Saalfeld:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Program#/Poster#: 174.07/UU28

Topic: I.02. Systems Biology and Bioinformatics

Support: R01EY014439

Title: Large-scale calcium imaging of the visual cortex in freely behaving, juvenile mice

Authors: *C. GROVES KUHNLE[1], K. B. HENGEN[5], S. E. RICHARDS[2], S. D. VAN HOOSER[3], G. TURRIGIANO[4]
[2]Neurosci., [3]Biol., [4]Dept of Biol., [1]Brandeis Univ., Waltham, MA; [5]Biol., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Studying the mechanisms by which individual or populations of neurons modify their activity based on sensory experience has historically been difficult to investigate in the living brain. While multi-channel electrodes used in rodents may permit recording from a wide range of number of cells, calcium imaging can provide the added benefits of monitoring up to hundreds of cells in stable spatial locations and the potential for recording the same cells over time. However, current protocols for calcium imaging with miniature endoscopes are optimized for adult mice, and recordings in juvenile animals, near the time of critical periods, are difficult. Here we demonstrate a protocol for tracking populations and individual cells longitudinally using a miniature endoscope and prism lens inserted into the primary visual cortex of juvenile mice. We inject an AAV vector expressing GCaMP6f into the cortex of neonatal mice (aged P0-P2) by hand, allowing viral expression to reach its maximum by the time animals enter the visual critical period. Additionally, our imaging solution requires inserting a prism lens (which is a GRIN lens with a triangular prism attached on the end) into the brain which permits imaging of active cells vertically across multiple layers of visual cortex. Consequently, for the first time to the best of our knowledge, we have reproducibly achieved stable imaging in several cohorts of young mice. Here, we will report progress on applying this technique to studying the impact of sensory perturbations on the development of neural circuits.

Disclosures: C. Groves Kuhnle: None. **K.B. Hengen:** None. **S.E. Richards:** None. **S.D. Van Hooser:** None. **G. Turrigiano:** None.

Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: NSF Grant 1257895

NIH 1R15HD077624-01

Title: Analysis of neural homeologous genes in the developing allotetraploid frog Xenopus leavis

Authors: *R. R. CUTLER, C. GOLINO, L. LO, M. POWNALL, L. BOLKHOVITINOV, C. DONG, J. GIRIBHATTANAVAR, M. SAHA
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Abstract: A convergence of two *Xenopus* diploid species in a polyploidization event 17-18 million years ago resulted in the allotetraploid *Xenopus laevis.* The *X. laevis* genome has been split into 2 diploid subgenomes denoted L and S, where 39% is made up of homeologous pairs - genes that are orthologous to the closest relative *X. tropicalis* and are both in the L and S subgenomes. While homeolog regulation has been characterized during normal development in important signaling pathway genes, little is known about the regulation of neural homeologs in response to developmental perturbation. Thus, our study explored the global patterns of homeologs in response to genetic and physical perturbations to the developing nervous system during neural developmental stages of *X. leavis* embryos. We conducted RNA-Seq experiments on developing *X. laevis* embryos that have been exposed to the following genetic or physical perturbations during development: (1) upregulation and downregulation of the Notch signaling pathway at the two-cell stage (2) anterior-posterior rotations (APR) of the neural axis at stages 11.5 and 12.5. RNA-Seq reads were mapped to the *X. laevis* genome assembly v9.1 using HISAT2 and counts were measured using HTSeq-Count with the UTA_MAYBALL gene model. Differential expression was measured using DESeq2 for both singletons and homeologs. We developed a homeolog specific analysis pipeline where 5041 homeologous pairs were identified and transcripts per million (TPM) were calculated for each homeolog. Preliminary analysis of Notch perturbation data has revealed both L and S specific biases in differentially expressed homeologs (DEH) for a large proportion of initial differentially expressed genes in upregulated conditions at stage 18 that diminish at stage 38. These data are grouped into ‘change in bias intensity’ or ‘onset of bias’ based on expression trends between homeologs. Across all conditions, a greater proportion of genes were biased towards L, which is consistent with normal development. In the APR experiment, embryos rotated at stage 12.5 and measured at stage 30 showed increased bias intensity towards S in the majority of DEH. Notably, there was a large onset of bias towards L for a single DEH in embryos rotated at stage 12.5 and measured at stages 30 and 18 respectively. We conclude that perturbations during neural development cause a significant transcriptome response that is largely characterized by variations in specific neural homeolog regulation to facilitate recovery. These findings highlight the complex regulatory patterns that have evolved since the polyploidization event and may contribute to developmental robustness.

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Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: Merit Review Award BX002343

NIMH R21MH103877

NIND R24NS092988

Title: Alterations of neuron-subtype-specific non-coding regulatory elements in the course of evolution of the primate prefrontal cortex

Authors: *A. KOZLENKOV[1,2], M. VERMUNT[3], P. APONTES[2], C. SHERWOOD[4], Y. L. HURD[1], W. BYNE[2], M. CREYGHTON[3], S. DRACHEVA[2,1]
[1]Dept. of Psychiatry, Mount Sinai Sch. of Med., New York, NY; [2]James J. Peters VA Med. Ctr., Bronx, NY; [3]Hubrecht Institute-KNAW and Univ. Med. Ctr. Utrecht, Utrecht, Netherlands; [4]Anthrop., George Washington Univ., Washington, DC

Abstract: Genome sequencing identified high similarity among coding regions of different primate species. Therefore, most of the phenotypic variation has been predicted to occur as a result of changes in regulation of gene expression due to functional alterations of non-coding cis-regulatory elements (CREs; such as promoters and enhancers).
Using low-input ChIP-seq assay, we performed whole-genome profiling of H3K27ac histone modification (which is indicative of active enhancers and promoters) in two major neuronal populations from the brains of three primate species (human, chimpanzee, and rhesus macaque). The autopsy tissues were obtained from the dorsolateral prefrontal cortex of clinically unremarkable adult individuals. Nuclei of the two major neuronal populations—projection glutamatergic neurons (Glu) and medial ganglionic eminence-derived GABAergic interneurons (GABA)—were obtained using fluorescence-activated nuclear sorting. H3K27ac profiling was complemented with neuron-subtype-specific transcriptome (nuclear RNA-Seq) from the same samples.
Unsupervised hierarchical clustering of the H3K27ac data revealed that the samples were first grouped based on their neuronal subtype followed by clustering according to species. As expected, human and chimpanzee samples were more similar to each other compared to macaque.
We detected numerous H3K27ac-enriched regions (putative CREs, hereafter denoted as CREs) that differ between the neuronal subtypes as well as among the species in each of the subtypes. Genomic annotation showed that a large proportion of CREs located distal to TSS (putative

active enhancers) differed among the species, whereas the proximal CREs (active promoters) were much more conserved. However, compared to the distal CREs, the promoter differentially enriched CREs showed significantly higher correlation with gene expression differences. Notably, the majority of CREs that were differentially enriched among the species were detected within neuron-subtype-specific CREs, suggesting that in the course of primate evolution most regulatory changes may occur in a cell-type-specific manner.
Compared to our previous studies that were performed in homogenate tissue samples and identified only a limited regulatory change after human-chimpanzee divergence, we now identified thousands of CREs that were differentially enriched in humans vs. chimpanzees and macaques in Glu or GABA neurons (human-specific CREs).
Overall, our findings underline the advantages of cell-type-specific epigenetic studies for the identification of regulatory changes that occurred in the brain in the course of primate evolution.

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Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.10/UU31

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF

NIH

NASA

Title: Nervous system-wide single cell RNA-seq of the *Drosophila* larva

Authors: *B. COCANOUGHER[1,2], J. WITTENBACH[3], J. YAN[3], L. AITCHISON[2], J. V. ALEMAN[1,2], A. B. KOHN[4], A. CARDONA[3], M. ZLATIC[3], S. C. TURAGA[3], L. L. MOROZ[4,5,6]
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Abstract: The brain relies upon a diversity of neuron types to process information; this is true in simple nerve nets of *C. elegans*, in compact insect nervous systems, and in the elaborate mammalian brain. Mapping variations in gene expression across space and time in the *Drosophila* nervous system has been a laborious process over the last half century, usually profiling single populations of cells based on one or a few genes or proteins. Here, we leverage

new high-throughput single-cell RNA sequencing techniques to generate the first whole nervous system gene expression profiles from *Drosophila* with single-neuron resolution. We collected 129,465 neurons and cells from peripheral tissues. Given that the *Drosophila* larva has a nervous system of approximately 10,000 cells, nearly all cells should be represented within this scRNA-seq profiling. Such a dataset in *Drosophila* is particularly powerful given the wealth of genetic tools for labeling specific cells and a well-annotated genome. Novel machine learning techniques were applied to investigate and classify cell classes and gene groups. These data allow us to understand gene expression at multiple scales, from single cells to the entire nervous system, explore the complexity of cell classes defined by clustering techniques, and provide a resource for further investigation into the structure and function of the *Drosophila* nervous system.

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Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Program#/Poster#: 174.11/UU32

Topic: I.02. Systems Biology and Bioinformatics

Title: Neurodata Without Borders: a framework for converting neurophysiology data to a standard format

Authors: *G. A. DENISOV[1], J. L. TEETERS[2], L. UMAYAM[1], K. SVOBODA[1]
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Abstract: Standardization of data formats is critical for efficient data sharing and reproducibility. Data sharing in standard data formats is routine in structural biology and genomics. Data standardization is particularly challenging in neurophysiology. The neurophysiology data have to be linked to complex behavioral data, sensory and optogenetic stimuli, as well as the metadata describing the experiment. The Neurodata Without Borders: Neurophysiology [1] is a project to develop a unified data format for cellular-based neurophysiology data, focused on the dynamics of groups of neurons measured under a large range of experimental conditions (Teeters et al., 2015) [2]. The format is used for extracellular neurophysiology, intracellular neurophysiology, and imaging experiments. Data from a single experimental session are stored in an HDF5 file with specific groups and datasets [3]. The main practical challenge in conversion of neurophysiology data from their original custom formats to the NWB format stems from the large variability in the source formats. We developed a Python-based framework [4] that facilitates conversion of neurophysiology data from their original

formats to the NWB format. Our approach involves two steps, with Python dictionaries being the intermediate data instances. The keys in these dictionaries are the full paths to the datasets in the target NWB file, and the values are the contents of the datasets. Conversion of each logically independent portion of data is implemented as a stand-alone task, producing a partial NWB file. The partial files are subsequently assembled automatically to produce the NWB file. We applied the conversion to two representative data sets uploaded to the online repository [5]: an extracellular electrophysiology data set (Li et al, 2015) [6] and a two-photon calcium imaging data set (Peron et al, 2015) [7]. We additionally illustrate the approach with didactic examples in Jupyter notebooks.

References:
[1] http://www.nwb.org/nwb-neurophysiology/
[2] http://dx.doi.org/10.1016/j.neuron.2015.10.025
[3] https://github.com/NeurodataWithoutBorders/specification
[4] https://github.com/NeurodataWithoutBorders/exp2nwb
[5] https://crcns.org/
[6] http://dx.doi.org/10.1038/nature14178
[7] http://dx.doi.org/10.1016/j.neuron.2015.03.027

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Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: JSPS KAKENHI 25560428

JSPS KAKENHI 26280110

JSPS KAKENHI 26280110

JSPS KAKENHI 15HP8038

JSPS KAKENHI 16HP8032

NIJC funding support to the ViBrism DB Committee

Title: ViBrism database for gene expression maps and co-expression networks analysis on the 3D brain

Authors: K. SHIMOKAWA[1], M. MORITA[2], M. NISHIMURA[2], H. YOKOTA[2], S. WEMLER[3], Y. OKUMURA[4], Y. YAMAGUCHI[4], *Y. OKAMURA-OHO[5,2,6]
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Abstract: ViBrism DB (http://vibrism.neuroinf.jp/) is a platform aiming at integration of information about brain architecture based on molecular distribution of many genes on the three dimensional (3D) anatomical context. Comprehensive gene expression densities in the mouse brain were measured with microtomy-based technology, which we invented, Transcriptome Tomography1, and were mapped on the 3D MRI space compatible to the mouse standard brain coordinate. Now 172,023 maps of overall gene expression in the three developmental stages after the birth and in the adult brain are searchable by gene IDs, and the results are shown as 2D/3D maps on the MRI images. Also, the measured densities at each stage are subjected to gene-by-gene correlation analysis of co-expression using Pearson correlation coefficient as a similarity measure2, and then co-expression search results can be browsed as network tables and graphs associated with the 2D maps. These frameworks enable to comprehensively assess expression patterns underlying brain structures and functions. ViBrism DB is a unique database for anatomy/function association based on gene expression.
Acknowledgement: This work was supported by members in RIKEN Neuroinformatics Japan Center (NIJC) and in the INCF Task Forces of the on Digital Brain Atlasing.

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Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: Merit Review Award (BX002343)

NIMH (R21MH103877)

NIH (R00NS080911)

Title: Cell-type-specific integrated analysis of the epigenome and transcriptome of human prefrontal cortex

Authors: *J. LI[1], A. KOZLENKOV[2,3], P. APONTES[2], Y. HURD[3], W. BYNE[2,3], E. A. MUKAMEL[1], S. DRACHEVA[2,3]
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Abstract: The diversity of neuronal and glial cells in the human brain is established and maintained through spatiotemporal regulation of gene expression by epigenetic programs. Despite the fundamental importance of this regulation, the genomic distribution of DNA methylation and its relationship with transcription in specific cell types are poorly understood. Using oxidative-bisulfite and bisulfite sequencing, we performed whole-genome DNA methylation and hydroxymethylation profiling of nuclei purified from three major cell types—glutamatergic (Glu) neurons, GABAergic (GABA) neurons, and oligodendrocytes (Olig)—obtained from human autopsy prefrontal cortex (PFC). This approach directly quantifies 5-methylcytosine (mC) and total methylation (tmC), which is the combination of mC and 5-hydroxymethylcytosine (hmC). hmC is estimated by subtracting mC from tmC. We complemented these data with cell-type-specific transcriptome (nuclear RNA-Seq) and active promoter/enhancer histone modification (H3K27ac) chromatin immunoprecipitation (ChIP) sequencing from the same samples. We then performed integrated epigenome and transcriptome analysis to elucidate the role of epigenetic modifications in regulating cell-type-specific gene expression.
We detected major differences among the cell types in the average levels of hmCG (Glu>GABA>Olig) and mCG (Olig>GABA>Glu). We found numerous differentially methylated regions (DMRs), with significantly more DMRs hypomethylated in Glu vs. GABA cells. tmCG and mCG levels were lower in regions marked by H3K27ac, whereas the percentage of hmCG was increased in these regions. While the level of tmCG within cell-type-specific distal H3K27ac peaks (indicative of enhancers) varied between the cell types (GABA>Glu>Olig), the level of mCG was low and similar in all cell types. This indicates that differences among the three cell types in tmCG in putative enhancers may be largely explained by differences in hmCG.
In both neuronal subtypes, gene expression was positively correlated with promoter H3K27ac signals and gene body hmCG levels, and negatively correlated with promoter mCG and gene body non-CG methylation (mCH) levels, with H3K27ac and gene body mCH being the strongest predictors. In Olig cells, which have much lower mCH than in neurons, promoter H3K27ac was the major predictor of gene expression, followed by gene body hmCG and promoter mCG levels. Overall our results revealed substantial genome-wide differences in DNA methylation and hydroxymethylation coordinated with cell type-specific transcription regulation across three major PFC cell types.

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Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: Munich Center for Systems Neurology EXC 1010

Center for Integrated Protein Science Munich EXC 114

European Research Council (ERC) FP/2007-2013 616791

EMBO Postdoc fellowship

Title: Probing mitochondrial diversity by isolating cell-type-specific mitochondria *In situ*

Authors: C. FECHER[1,3,4,5], L. TROVÓ[1,4,7], J. WETTMARSHAUSEN[6], S. A. MUELLER[7,2], N. SNAIDERO[1,4], O. ORTIZ[8], S. HEINK[10], T. KORN[10,4], W. WURST[8,4,7], S. F. LICHTENTHALER[7,4], F. PEROCCHI[6,4,9], *T. MISGELD[11,3,4,7]
[1]Inst. for Neuronal Cell Biol., [2]Neuroproteomics, Tech. Univ. of Munich, Munich, Germany; [3]Ctr. of Integrated Protein Sci. (CiPSM), Munich, Germany; [4]Munich Cluster for Systems Neurol. (SyNergy), Munich, Germany; [5]Grad. Sch. of Systemic Neurosci., [6]Gene Ctr. Munich, Ludwig-Maximilians-University of Munich, Munich, Germany; [7]German Ctr. for Neurodegenerative Dis., Munich, Germany; [8]Inst. of Developmental Genet., [9]Inst. for Obesity and Diabetes, Helmholtz Zentrum München, Munich, Germany; [10]Dept. of Neurol., Klinikum rechts der Isar, Tech. Univ. of Munich, Munich, Germany; [11]Technische Univ. München, Munich, Germany

Abstract: While mitochondria serve the bioenergetic needs of cells in most vertebrate tissues, they fulfill additional functions, e.g. calcium homeostasis and regulation of apoptosis. When comparing different tissues or cell types, mitochondria have remarkably diverse morphologies and dynamics that may reflect distinct functions imposed by host cell requirements. Nonetheless, little is known about the molecular heterogeneity that underlies the different functions and shapes of these organelles. Therefore we set out to develop a tool that would allow probing mitochondrial diversity between different cell types *in situ*.
To address this, we generated a reporter mouse in which mitochondria are tagged with an outer mitochondrial membrane GFP (GFP-OMM) in a Cre-dependent manner. In addition, we developed an immune-capture protocol that allows us to enrich GFP-tagged mitochondria. We demonstrate (1) that GFP-OMM expression is organelle-specific and faithfully depends on Cre-expression in these reporter mice, (2) that the transgene neither alters mitochondrial morphology nor interferes with mitochondrial dynamics and function, (3) that we can isolate mitochondria in

a cell-type-specific manner while avoiding cross-contamination with unlabeled mitochondria and (4) that our approach yields sufficient material from various neural cell types to perform functional characterization of immune-captured mitochondria using respiratory measurements as well as unbiased analyses, such as proteomic characterization.
As proof-of-principle we compare mitochondria from Purkinje cell and astrocytes in the adult cerebellum using proteomics and identify previously reported and novel mitochondrial proteins that are enriched in a cell-type-specific manner. Furthermore the data allows predicting metabolic and functional differences related to mitochondrial biology which we are currently further investigating. In the future, our approach will help to explore the molecular diversity of mitochondria and identify cell-type-specific, mitochondria-related pathways in development, aging and diseases.

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Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH P20GM103643

Title: 3' untranslated region transcript variation in neuroplasticity

Authors: *B. J. HARRISON
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Abstract: mRNA 3'-untranslated regions (3'UTRs) regulate gene functions by modifying cellular localization, stability and/or translational efficiency of transcripts during normal biological functions (e.g., development, nervous system functions) and disease states (e.g., UTR shortening in cancer). 3’UTR isoform diversity is primarily generated by alternate polyadenylation (APA) during mRNA biosynthesis, providing a dynamic substrate for RNA-binding proteins (RNAbps), ribonucleoprotein aggregates and miRNAs. The recent surge in whole transcriptome sequencing studies has revealed an unexpected diversity and specify of regulation of 3’UTRs, and current estimates suggest there may be up to 5,000 genes with unannotated 3’UTR isoforms. Accurate measurement of 3’UTR transcript variation remains an unresolved challenge. Current methods either rely heavily on incomplete annotation data and/or employ statistical models sensitive to UTR shortening events at the expense of lengthening events. To address these limitations, we developed a novel computational method and

comprehensive analysis pipeline method to assess 3'UTR dynamics in RNA-Seq data. This approach was then employed to detect and quantify 3'UTRs dynamics from the *in vivo* peripheral afferent collateral sprouting model of axonal plasticity. We characterised approximately 2,000 previously unreported 3'UTR variants in these neurons, of which more than 200 were regulated upon induction of plasticity. Further computational analyses of these dynamic 3'UTR sequences revealed strongly over-represented motifs for neuron-specific miRNAs and RNA-binding proteins with known roles in nervous system pathologies. These studies demonstrated the utility of our method to assess 3'UTR dynamics with standard mRNA sequencing protocols. In addition, our analyses suggest that 3'UTR variants may control neuroplasticity through interaction with regulatory miRNA's and RNA-binding proteins.

Disclosures: B.J. Harrison: None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.16/UU37

Topic: I.02. Systems Biology and Bioinformatics

Support: Moody Project for Translational TBI Research

Darrell K Royal Fund for Alzheimer's Research

Mission Connect, a program of TIRR

NIH BD2K Road Trip

NINDS Grant NS067092

Veteran's Administration

Title: Big data approaches for diverse preclinical TBI research

Authors: *B. E. HAWKINS[1,2], J. L. NIELSON[4,5], J. WOLF[2], C. R. ANDERSEN[3], H. M. SPRATT[3], J. HUIE[4], D. S. DEWITT[2], D. S. PROUGH[2], A. R. FERGUSON[4,6]
[2]Anesthesiol., [3]Dept. of Preventive Med. and Community Hlth., [1]Univ. of Texas Med. Br., Galveston, TX; [4]Brain and Spinal Injury Ctr., Univ. of California San Francisco, San Francisco, CA; [5]San Francisco Veteran's Admin. Med. Ctr., San Francisco, TX; [6]San Francisco Veteran's Admin. Med. Ctr., San Francisco, CA

Abstract: The objective of this collaborative study is to provide a proof-of-concept of modern data science tools applied to existing high-density data repositories of preclinical animal studies in traumatic brain injury (TBI) for novel translational discoveries. Multi-modal data from graded

TBI injuries with varied treatment conditions were gathered from Moody Project for Translational TBI Research studies in rodents. In a chronic time course study of parasagittal fluid percussion injured rodents, long term learning and memory deficits persist up to one-year post TBI. To convert these big-data to knowledge and to elucidate connections between behavior and histopathologic, genomic and proteomic changes post TBI, the Moody Project PIs launched a collaboration with data scientists with expertise in preclinical and clinical neurotrauma data. The main purpose of this effort is to create an example repository of completed studies in preclinical TBI, and develop syndromic analytical workflows that 1) capture both the complexity of the study design and 2) render outcome testing through multidimensional machine learning approaches to increase the effect size resolution for hypothesis testing of treatment trials. Prior applications of these methodologies to preclinical TBI and clinical TBI have demonstrated utility of multiscalar ‘omics (syndromics) for TBI and spinal cord injury (SCI). The current study aims to expand upon these efforts, capturing the full spectrum of bio-behavioral and molecular changes that result from TBI, and help resolve treatment approaches that reproduce results across diverse endpoints, increasing potential for translation into clinical trials in humans. These studies were supported in part by the Darrell K Royal Research Fund for Alzheimer’s Disease (BEH), Mission Connect, a Program of TIRR (BEH), Moody Project for Translational TBI Research (DSP and DSD), NIH BD2K RoAD-Trip Fellowship (BEH with ARF), NINDS Grant NS067092 (ARF) and Veteran's Administration Grant (ARF).

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Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH Grant EB13571

Title: Imaging mRNAs in living animals

Authors: *H. LIM[1], C. NWOKAFOR[2], R. H. SINGER[3]
[1]Hunter Col., New York, NY; [2]Albert Einstein Col. of Med., New York, NY; [3]Anat. & Structural Biol., Albert Einstein Col. of Med., Bronx, NY

Abstract: We report visualization of mRNAs in living animals. Intravital two-photon microscopy was performed on knock-in mice whose β-actin mRNAs contained MS2 binding sites (MBS) and MS2 binding protein fused to a fluorescent protein (MCP-XFP) was expressed

via lentiviral infection. We demonstrated cell-type-specific or intracellularly compartmentalized labeling of mRNAs to measure the dynamics of nascent transcripts and cytoplasmic mRNAs, which is useful for elucidating their roles in physiology.

Disclosures: H. Lim: None. **C. Nwokafor:** None. **R.H. Singer:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.18/UU39

Topic: I.02. Systems Biology and Bioinformatics

Support: Arnold and Mabel Beckman Foundation Young Investigator Grant (to P.N.)

COSMOS Club Foundation Fellowship (to S.C.)

Title: Bottom-up proteomics of limited neuron populations by microanalytical mass spectrometry

Authors: S. B. CHOI[1], *P. NEMES[1], M. ZAMARBIDE[2], M. MANZINI[2]
[1]Dept. of Chem., [2]Dept. of Pharmacol. and Physiol., George Washington Univ., Washington, DC

Abstract: Characterization of the proteome facilitates the understanding of molecular mechanisms involved during neuronal development in the nervous system. However, detection of proteins in small populations to a handful of neurons is challenging due to sensitivity limitations in current mass spectrometry (MS). Here, we present microanalytical MS to enable ultrasensitive characterization of proteins from limited neuron populations cultured from the mouse hippocampus. We integrate custom-built capillary electrophoresis (CE) nanoelectrospray ionization (nanoESI) MS with a data-dependent acquisition (DDA) to allow trace-level detection capability. This approach is able to detect ~260 zmol (156,000 copies) of model peptides, such as angiotensin II and ~15 amol (1 pg) of model proteins, including bovine serum albumin or cytochrome c. We utilized this platform to identify proteins from ~500 pg of protein digest from hippocampal neurons, which estimates to the total protein content from a handful of neurons. By programming DDA to progressively exclude high-intensity peptides from sequencing ("DDA ladder"), CE-ESI-MS enabled the identification of 361 non-redundant protein groups from ~500 pg protein digest. These proteins spanned a 4-log order dynamic range in concentration and included products from genes that are classical neuronal markers, such as those involved in neurotransmitter exocytosis (e.g., Syn1, Snap25, and Syt1) neuronal-specific cytoskeletal components (e.g., Ina, Map2). We also identified proteins that have been implicated in neurodegenerative disorders. For example, microtubule-associated protein tau (Mapt) is accumulated in the brain of patients with Alzheimer's diseases, and alpha-synuclein (Snca) is

mutated in frontotemporal dementia with Parkinsonism. Combined, ultrasensitive CE-nanoESI-MS with DDA ladder opens a new gate to query cell-type specific gene translation during early brain development.

Disclosures: S.B. Choi: None. **P. Nemes:** None. **M. Zamarbide:** None. **M. Manzini:** None.

Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIH R01GM114851

Title: A novel approach to rapidly identify systemic immune patterns after cardiac arrest and resuscitation: A t-SNE analysis

Authors: N. R. BRANDON[1], H. DOU[2], *Y. XU[1]
[1]Anesthesiol., Univ. Pittsburgh Sch. Med., Pittsburgh, PA; [2]Dept. of Biomed. Sci., Texas Tech. Univ. Hlth. Sci. Ctr. - El Paso Campus, El Paso, TX

Abstract: Most experimental treatment strategies for cardiac arrest (CA) have failed clinically. An overlooked element is the systemic immune response, which both exacerbates injury and promotes recovery in a time-dependent manner. Correlations between peripheral immune responses and brain injuries are of diagnostic value in guiding therapeutic interventions. Using t-distribution stochastic neighbor embedding (t-SNE), a machine-learning algorithm, we analyzed multidimensional immune markers in various organs by flow cytometry and determined the up- and down-regulation of immunocyte subsets in the t-SNE space due to cardiac arrest. By minimizing the divergence in representing high-dimensional association with low-dimensional display in t-SNE space, this approach allows non-obvious or even counter-intuitive pattern changes to be discovered.
A clinically relevant cardiac arrest and resuscitation model, mimicking human cardiopulmonary support, was performed on Balb/c mice to produce 6-min of CA. Naïve and sham controls are also analyzed. After recovering for 1, 3, or 5 days after resuscitation, mice were sacrificed and their liver, spleen, and bone marrow were collected for flow cytometric analysis. The lymphocytic markers included CD3, CD4, CD8, CD25, CD28, and CD45. The phagocytic markers included CD45, CD11b, CD11c, CD80, CD86, F4-80, Ly6C, and Ly6G.
The data from the lymphocytes and phagocytes were each concatenated by day, down sampled to 100,000 cells, and analyzed using the t-SNE plugin in FlowJo. The t-SNE space revealed distinct gains of expression (GOE) that are unique to cardiac arrest but absent in the naïve and sham controls. Equally important are the losses of expression (LOE) that are distinctive in the naïve

and sham controls but are lost after cardiac arrest and resuscitation. The most profound changes in the lymphocytic dimensions are the GOE of associations among $CD45^{hi+}CD3^{+}CD4^{+}CD25^{+}CD28^{+}$ in the spleen, the LOE of $CD4^{+}CD25^{+}CD28^{+}$ association in the liver, and the GOE of $CD4^{+}CD8^{+}CD45^{+}CD25^{+}CD28^{+}$ association in the bone marrow. The phagocytic dimensions are characterized by the LOE of a singly $CD45^{hi+}$ population in the naïve spleen and liver, and the GOE of two clusters of all positive and all negative phagocytic markers in the liver. An area associated with $CD11c^{-}$ and positive for the rest of the seven markers is visible as a GOE in the bone marrow. The t-SNE analysis is a powerful tool to rapidly identify salient differences among various experimental groups in an unbiased manner. This establishes a clinically applicable and useful tool as the foundation for future diagnostic tests and therapeutic interventions in treating cardiac arrest patients.

Disclosures: **N.R. Brandon:** None. **H. Dou:** None. **Y. Xu:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

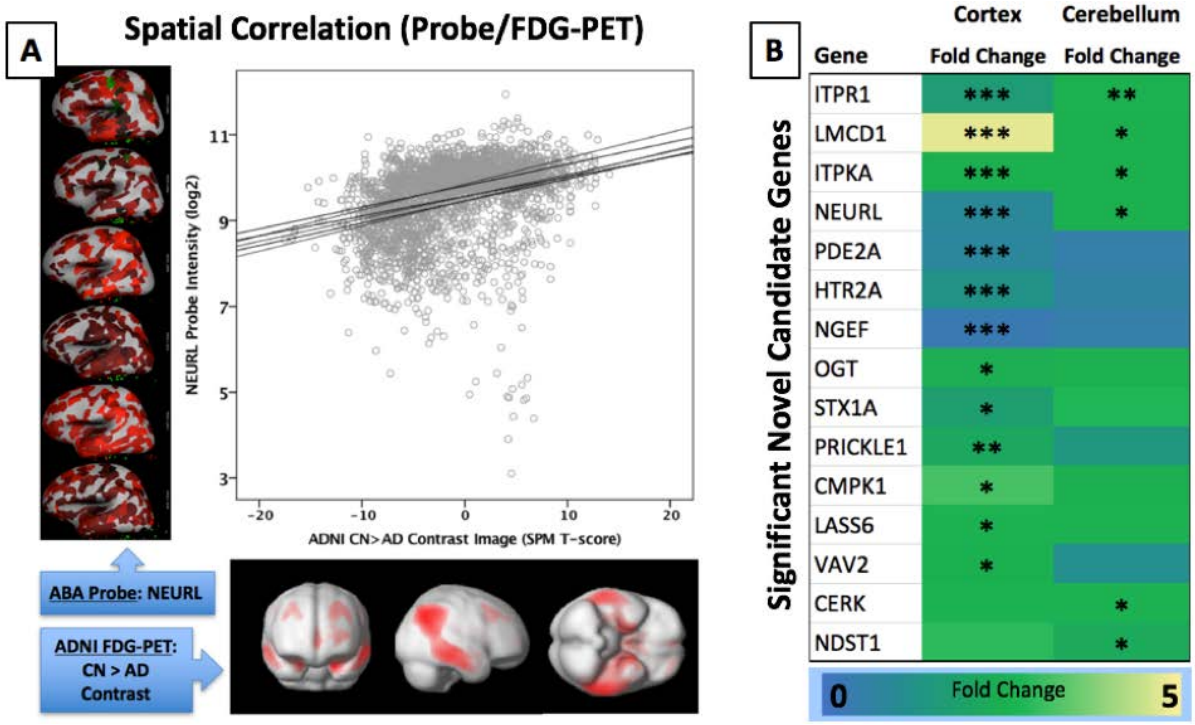
Support: This research was supported entirely by the Intramural Research Program of the NIH, National institute on Aging.

Title: Validation of a data-driven neuroinformatics approach to identifying novel candidate genes for Alzheimer's disease

Authors: *R. J. MULLINS, E. HUTCHISON, E. EITAN, A. ALAGHATTA, M. WILSON, J. WILLIAMSON, M. MATTSON, D. KAPOGIANNIS
Lab. of Neurosci., Natl. Inst. On Aging, Baltimore, MD

Abstract: Data-driven methods for identifying genes involved in Alzheimer’s disease (AD) pathogenesis aim to complement hypothesis-driven approaches that reflect current theories about the disease. We present an unbiased approach based on inter-correlated features between multi-modal 3D brain images. We hypothesized that regional differences in gene expression may modulate susceptibility to AD. Using a custom MATLAB script, we correlated the spatial expression of 20,786 unique gene microarray probes from each of the six specimens in the Allen Human Brain Atlas (AHBA) with a fluorodeoxyglucose-positron emission tomography (FDG-PET) contrast image of AD-related brain hypometabolism in 241 AD participants and 288 age-matched controls from the Alzheimer’s Disease Neuroimaging Initiative (ADNI, Figure A). To explore the pathogenic relevance of these findings and validate the approach, we selected twenty-six “candidate” genes from the highest significant results of this approach and four

“canonical” genes widely accepted as AD-related for comparison. These 30 genes were tested using qRT-PCR on post-mortem human inferior parietal cortex and cerebellar tissue from 8 AD and 8 age-matched control specimens. Half (13) of the novel candidate genes showed significantly different expression in the parietal cortex of AD subjects compared to controls (Figure B), as well as 3 of the canonical genes. Only six candidate genes differed in AD cerebellum compared to control. The consistent association of these candidate genes with the regional pattern of AD-related hypometabolism and differential expression in AD-vulnerable brain areas suggests that this data-driven methodology is an effective method for identifying promising novel candidate genes for AD. This research was supported entirely by the Intramural Research Program of the NIH, National institute on Aging.



Disclosures: **R.J. Mullins:** None. **E. Hutchison:** None. **E. Eitan:** None. **A. Alaghatta:** None. **M. Wilson:** None. **J. Williamson:** None. **M. Mattson:** None. **D. Kapogiannis:** None.

Poster

174. Systems Biology and Bioinformatics

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Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.21/UU42

Topic: I.02. Systems Biology and Bioinformatics

Support: IRP-NIMH

Title: Regulation of the human dopamine transporter (hDAT) from a full-length model perspective

Authors: M. FENOLLAR FERRER, *S. G. AMARA
Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Monoamine transporters limit signaling between neurons by clearing synaptically-released neurotransmitters. These transporters belong to the solute carrier family 6 (SLC6), which includes the serotonin transporter (SERT), norepinephrine transporter (NET) and the dopamine transporter (DAT). The function of these proteins is highly regulated primarily by protein-protein interactions that involve the cytoplasmic tails (N- and C-terminal domains) of the carriers. Alterations in the function of monoamine transporters have been linked to neuropsychiatric disorders such as depression, OCD, and schizophrenia. Although some structural data on the transmembrane domains of these transporters has recently emerged with the high-resolution X-ray structures of the *drosophila* DAT (dDAT), human SERT (hSERT) and the bacterial analog LeuT, little structural information is available on the N- and C-terminal cytoplasmic domains of these proteins. Here we present a new computational protocol, which was used to obtain a full-length model of the dopamine transporter. This model will allow the study of the intracellular regulatory processes governing DAT function and will characterize at atomic resolution the protein-protein complexes involved in these different pathways. This approach will establish a basis for the future development of new drugs for modulating the network of proteins that regulate dopamine transporter functions.

Disclosures: M. Fenollar Ferrer: None. **S.G. Amara:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

Support: NIMH U01MH105971

Title: Denoising high density gene expression in whole mouse brain images

Authors: A. VADATHYA[1], *K. UMADEVI VENKATARAJU[2], K. MITRA[1], P. OSTEN[2]
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Abstract: Image Analysis of gene expression data in model animals is key to understanding the distribution of cell types in their brains. Many times the cellular/nuclear gene expression is in the same channel containing the anatomical features used for registration to a template brain. In that

case, the increased expression density affects local pixel intensity of down sampled anatomical features. We propose to use a deep generative network model for denoising the gene expression in the anatomical image channel to improve the registration accuracy in these image data sets.Recently, deep learning has shown a lot of promise for many image restoration tasks denoising, inpainting, super-resolution and deblurring. Especially, using generative image modeling frameworks like Generative adversarial nets (GANs), Pixel Recurrent Neural Nets (PixelRNN) and Recurrent Image Density Estimator (RIDE) people have shown impressive image inpainting results both at high level (missing contents) and low level (missing pixels). RIDE and PixelRNN employ recurrent networks to model image distribution in an autoregressive fashion. Using Long Short Term Memory (LSTM) recurrent units we achieve state of the art image generative models. We tackle the problem of gene expression denoising by training a deep generative network and learning an image prior from the Serial two-photon tomography images at 1 micron resolution. We learn this image prior using LSTM recurrent units following the approach of RIDE. The distribution of current pixel is conditioned on the past pixels which are compactly represented through LSTM hidden states. The network parameters are trained by minimizing model's negative log-likelihood (NLL) score over the training images. Finally, we mask the fluorescence expressing nuclei in the given brain images and inpaint these masked regions using the learned image prior thus achieving virtually expression free downsampled images for image registration.

Disclosures: **A. Vadathya:** None. **K. Umadevi Venkataraju:** None. **K. Mitra:** None. **P. Osten:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Topic: I.02. Systems Biology and Bioinformatics

Support: R01DK104363

R01NS50465

Title: Single cell genomic analysis reveals vulnerable cell types and pathways to brain trauma

Authors: *D. ARNESON[1,2], H. BYUN[1], Y. ZHUANG[1], I. AHN[1], Z. YING[1], F. GOMEZ-PINILLA[1,3], X. YANG[1,2]
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Abstract: Concussive brain injury, a mild type of TBI (mTBI), is common in sports, military, and domestic environments that often leads to neurological and psychiatric disorders. Currently there is no information on how TBI affects specific cell types and their genes responsible for the pathogenesis, thereby hindering the understanding of mechanisms involved and the development of treatments. Here we applied high throughput parallel single-cell sequencing using the cutting-edge Drop-seq to capture the transcriptomes of thousands of individual cells to objectively define cell types that are vulnerable to mTBI. We used systems biology to determine the multiple interactions between specific cell types and genes in the mouse hippocampus 24 h after moderate fluid percussion injury. We retrieved known major cell types in the hippocampus as well as previously uncharacterized cell clusters, and identified cell type-specific and pan-hippocampal differential sensitivity to mTBI. Interestingly, we identified two types of cell clusters not previously described that seem specific to the effects of TBI. TBI promoted major transcriptomic reprograming in ependymal, endothelial, astrocytes, oligodendrocytes, microglia, and subtypes of neurons (GABAergic, dentate gyrus). Cell-type specific pathways such as metabolic depression in astrocytes and amyloid-related pathways across multiple cell types were found to be perturbed by mTBI. We also conducted cell-cell connectivity analysis through gene coexpression between different cell types and found disrupted cell communications after mTBI. We identified *Ttr* as a pan-hippocampal marker upregulated in most cell types. Our findings show that TBI affects specific cell types that can be starter points of the pathology, and offer insights into how cell-type specific processes can be harnessed to design new strategies to redirect the course of mTBI and overcome subsequent brain disorders.

Disclosures: D. Arneson: None. **H. Byun:** None. **Y. Zhuang:** None. **I. Ahn:** None. **Z. Ying:** None. **F. Gomez-Pinilla:** None. **X. Yang:** None.

Poster

174. Systems Biology and Bioinformatics

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Topic: F.07. Autonomic Regulation

Support: NIH Grant R01 HL111621-01A1

NIH Grant T32 AA007463-28

Title: The transcriptional response of isolated single neurons in the dorsal motor nucleus of the vagus to the development of ischemic heart failure

Authors: *J. GORKY, R. VADIGEPALLI, J. S. SCHWABER
Thomas Jefferson Univ., Philadelphia, PA

Abstract: The dorsal motor nucleus of the vagus (DMV) has been shown to exert a protective effect against damage from myocardial infarction (MI) that may be crucial in preventing subsequent heart failure. A time series of transcriptional changes in neurons and DMV tissue was studied in a rat model of MI. The results show a significant response after 1 week involving Npff and histamine signaling in neurons. In DMV tissue more broadly, changes in oxytocin and dopamine receptors were noted. After 3 weeks, there were changes in somatostatin signaling not seen at 1 week. Several of these responses showed left/right asymmetry, with a bias toward changes on the right. Gene regulatory network topology was also significantly altered, showing the potential for the orexin-2 receptor to be a novel regulatory hub. We also show that Cav2.1 expression may influence much of the network behavior in the DMV. This represents the first time single neurons in the DMV have been transcriptionally assayed in response to ischemic heart failure and the results suggest new ways in which the DMV is regulated and in turn modulates protective effects at the heart.

Disclosures: J. Gorky: None. **R. Vadigepalli:** None. **J.S. Schwaber:** None.

Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: grant from the Collaborative Center for X-linked Dystonia Parkinsonism (CCXDP)

a gift from T. and V. Stanley

Title: Not by systems alone: identifying functional outliers in rare disease pedigrees

Authors: *S. BALLOUZ[1], M. DöRFEL[1], J. CRAIN[1], M. CROW[1], G. J. LYON[1,2], J. GILLIS[1]
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Abstract: A systems biology approach to disease expression analysis typically involves looking for shared functional signals among a set of genes exhibiting differential expression. Such approaches have been particularly prominent in the study of neuropsychiatric disease, due to their complexity, heterogeneity, and the challenge of finding convergent signals. But what does the typical systems approach miss? Here, we examine the possibility that disease genes display “outlier” or unexpected expression rather than reflecting a collective pattern of dysregulation, with a focus on the rare neurospychiatric disease, *TAF1* syndrome. We have collected and sequenced one quad and five trios from the *TAF1* syndrome cohort, a rare X-linked disorder genetically characterized by variants in the *TAF1* transcription factor. Affected individuals share

many phenotypic features, including facial dysmorphology, intellectual disability, global developmental delay, hypotonia, and other neurologic features. As we are looking for unusual differential expression in a disease context, we were able to design a novel family-specific differential expression analysis which exploits expected overlaps and differences in the transcriptomic profiles of the parents relative to their affected child. By tallying co-expression patterns from over 3000 expression samples in 75 experiments, we generated a frequency of common expression value for all gene pairs across most of the genome. Genes with jointly common expression values were then filtered away, leaving us with a small number of what we called "outlier" genes, characteristic of each proband. We then looked for recurrence of these genes across our cohort. We first find that filtering common co-expression removes almost 2/3rds of differential expression results and all GO functional enrichment of each proband. Importantly, we found a single outlier gene, the calcium channel subunit *CACNA1I*, that recurs in five of the six pedigrees. Notably, this gene is recurrently implicated in other neurological diseases such as schizophrenia and autism, making it a very plausible candidate. The sole family in which no signal was present was a CNV carrier, whilst the other probands had different single nucleotide variants, implying a potentially different underlying molecular mechanism. Our outlier-based analysis revealed otherwise difficult to observe signals in the case of *TAF1* syndrome cohort, and we anticipate that future transcriptomic studies of rare disorders would benefit from this type of analysis.

Disclosures: **S. Ballouz:** None. **M. Dörfel:** None. **J. Crain:** None. **M. Crow:** None. **G.J. Lyon:** None. **J. Gillis:** None.

Poster

174. Systems Biology and Bioinformatics

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Topic: I.02. Systems Biology and Bioinformatics

Support: CIRM

Biohub

NSF GRFP

Title: A comprehensive molecular atlas of striatal projection neurons by single-cell rna-seq

Authors: *G. STANLEY[1], O. GOKCE[2], B. TREUTLEIN[3], R. C. MALENKA[4], P. E. ROTHWELL[5], M. V. FUCCILLO[6], T. C. SUDHOF[7], S. QUAKE[1]
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Germany; [4]Stanford Inst. for Neuro-Innovation & Translational Neurosci, Stanford Univ. Sch. of Med., Palo Alto, CA; [5]Neurosci., Univ. of Minnesota, Minneapolis, MN; [6]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [7]Stanford Univ., Stanford, CA

Abstract: The brain contains the largest variety of cell types and anatomy of any organ in the mammalian body, and fully understanding the brain will require a comprehensive atlas of its cell types. Here, we combine single-cell RNA-Seq, rigorous computational approaches, and quantitative RNA *in situ* to create a comprehensive atlas of the transcriptional identities of striatal medium spiny neurons (MSNs). The striatum is a large, anatomically complex brain region, but 95% of its neurons are classified into one of just two canonical types: direct- or indirect-pathway medium spiny projection neurons (D1- or D2-MSNs). With the computational approach we developed - linear, iterative RPCA - we find that MSNs are comprised of three discrete subtypes: two canonical subtypes expressing either the D1 or the D2 dopamine receptor and a third, novel subtype which coexpresses canonical D1 and D2 dopamine receptors and neuropeptides. Within each of the three discrete subtypes, neurons exhibit continuous transcriptional heterogeneity, where gene expression is gradient-like rather than on/off, and many cells have intermediate expression levels of the marker genes. With quantitative RNA *in* situ, we show that these transcriptional continua typically encode anatomical gradients, where the expression levels of marker genes correspond directly to position along an anatomical vector. Each discrete subtype contained up to 12 such transcriptionally defined anatomical compartments, ranging from the ventral islands of Calleja to the dorsal striosomes. The remarkable concordance between continuous transcriptional identity and anatomical location in striatal MSNs suggests that this may be a general principal in the brain. Our work is now addressing the developmental origins of continuous vs. discrete neuronal identities and the roles of the genes involved in forming the complex anatomy of the brain.

Disclosures: G. Stanley: None. **O. Gokce:** None. **B. Treutlein:** None. **R.C. Malenka:** None. **P.E. Rothwell:** None. **M.V. Fuccillo:** None. **T.C. Sudhof:** None. **S. Quake:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

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Program#/Poster#: 174.27/UU48

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R01

Title: Novel *In vitro* model of aging identifies specific histone modifications in rat cortical cells

Authors: *L. RUOXU[1,2], B. MCCLARTY[1], G. RODRIGUEZ[1], A. SANZ-CLEMENTE[3], H. DONG[1]

[1]Psychiatry and Behavioral Sci., Northwestern Univ. Feingberg Sch. of Medici, Chicago, IL; [2]Beijing Inst. of Basic Med. Sci., Beijing, China; [3]Pharmacol., Northwestern Univ. - Chicago, Chicago, IL

Abstract: Aging has a strong influence on behavior in response to environmental stimuli, and changing gene expression is central to this phenomenon. During aging, epigenetic alterations accumulate, alter gene transcription, and make animals more vulnerable to noxious stimuli and more susceptible to adverse effects. While these epigenetic alterations are found in all aging cells, the impact of these changes are especially penetrant in terminally differentiated cells, such as neurons. Our previous work has demonstrated that well-characterized epigenetic marks, namely histone modifications, accumulate in specific brain regions and at specific gene promoters to alter behavioral responses in mice. However, *in vivo* investigations are time consuming, highly variable, and are generally prohibitive for studying changes in individual cells. Therefore, we sought to establish an in vitro model of cortical cell aging and characterize which histone modifications differ between aged and young cortical rat neurons.
We prepared primary neuronal cultures from the cortex and hippocampus of E18-19 Sprague-Dawley embryos of both sexes and maintained those cells in serum-fee neurobasal medium with b-27 and glutamine. At 7 or 42 DIV, cells were harvested and related histone modification markers (H3K9ac, H4K12ac, H3K27ac, H3K27me3 and H3K18ac) and SIRT6 were assayed via western blot. These results were compared with data of histone modification from cortical tissues obtained from young (2mo) and aged (22mo) mice. Western blot analyses indicate that H3K18ac, H4K12ac, H3K9ac, and SIRT6's expression in DIV 42 cells were significantly decreased in comparison to DIV 7 cells. Cortical tissue revealed an upregulation of H3K27me3 while SIRT6, H3K9ac, and H4K12ac was significantly decreased in aged compared to young mice. H3K18ac remain constant in those tissues. In total, SIRT6, H3K9ac, and H4K12ac were stably decreased in both aged tissue and cortical cells aged *in vitro*. Cultured aged cells displayed many similar histone modifications as aged cortical tissue when compared to young controls. In particular, a decrease in SIRT6, a stress responsive protein involved with DNA repair, may indicate a similar aging process leading to cell senescence. This work demonstrates that our *in vitro* aging culture captures many of the epigenetic alterations associated with aging. Future investigations will utilize this culture system to isolate DRD2-GFP neurons, which are highly implicated in psychological behavior and antipsychotic drug action.

Disclosures: L. Ruoxu: None. **B. McClarty:** None. **G. Rodriguez:** None. **A. Sanz-Clemente:** None. **H. Dong:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.28/DP13/UU49 (Dynamic Poster)

Topic: I.02. Systems Biology and Bioinformatics

Support: Grant-in-Aid for Research Activity Start-up to MS from MEXT (The Ministry of Education, Culture, Sports, Science and Technology)

Title: Cognition and micro-connectomics

Authors: A. NAKAMURA[1], *M. SHIMONO[2]
[2]Grad. Sch. of Engin. Sci., [1]Osaka Univ., Toyonaka, Japan

Abstract: Various cognitive functions of our brain are realized by interactions among a large number of neurons. Traditionally, the selectivity of neuronal activity to individual cognitive tasks has been studied. In order to understand the function of the brain more deeply, we need to investigate the micro-connectome, which is a comprehensive map of connectivity or interactions of neurons or synapses, beyond the basic statistical observations of its individual elements. This study reports the interactions among neurons measured from the anterior lateral motor cortex (ALM) of mice using calcium fluorescence imaging and focuses on selectivity for cognitive planning of directed licking behaviors. We reconstructed the functional networks from the spiking activities of the neuron ensembles at resting periods and compared them with the motion-selectivity of individual neurons. The network structure was characterized using graph theory. We will report a micro-connectomic approach that can extract unknown designs of micro-circuits of neurons and how this approach will contribute to a better understanding of the effects of aging and neuronal degeneration disease.

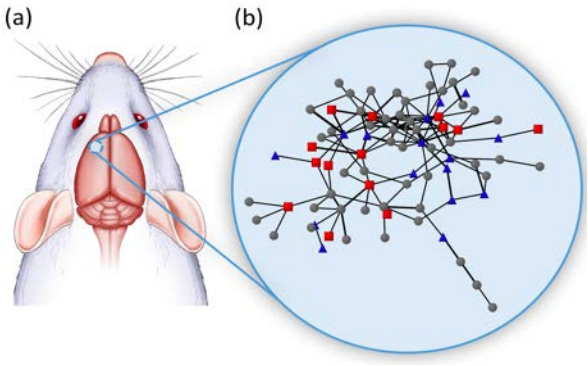

Figure 1: The general concept of this study. (a) Neuronal activities when rodents are taking rest (or just waiting a task) or when performing licking tasks were recorded using Ca Imaging technique. (b) is an example of effective/functional networks of neurons reconstructed from the neuronal dynamics. The differences of markers show differences of responses of neurons. (Neurons responding selectively to contralateral lickings (Δ), to ipsilateral lickings (□), and neurons showing no responses to these licking behaviors (○)).

Disclosures: A. Nakamura: None. **M. Shimono:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.29/UU50

Topic: I.02. Systems Biology and Bioinformatics

Title: Xeno-free induced pluripotent stem cell research: Advancing standards, best practices and discovery through an open toolkit

Authors: *A. LAM[1,2], F.-Y. LI[1], A. R. MUOTRI[3], E. L. OHAYON[2]
[1]Physicians Committee For Responsible Med., Washington, DC; [2]Green Neruoscience Lab., Neurolinx Res. Inst., San Diego, CA; [3]Pediatrics/Cellular Mol. Med., UCSD, La Jolla, CA

Abstract: The field of human-induced pluripotent stem cell (iPSC) research is rapidly growing and offers great promise for our basic understanding of neural mechanisms as well as therapeutic applications. However, both in basic science and clinical-relevant research, there is need of greater transparency and reproducibility in the iPSC methodology. Moreover, much of the current research still extensively uses xenogenic materials (components of animal origin), which affects the value of these studies. Specifically, it is well known that components of animal-origin are highly variable, carry risks of transferring pathogens and/or unwanted biological material to the model system thereby unnecessarily reducing the predictive value of the research. Previously we have reported the ongoing development of an online toolkit that can address these issues by supporting broader access and refinement of xenofree protocols. Here we extend the application by explicitly addressing the dimension of standards and replicability. In order to identify the specific gaps in xenofree implementation in iPSC research we have examined existing guidelines and studies which have followed Good Manufacturing Practices, good laboratory practices and efforts for standardization. Our preliminary findings show that the process of standardization of design, practice, interpretation and report of iPSC research are still very much in their infancy. Moreover, the awareness of the availability of non-xenogenic materials and the understanding of the need of xenofree research remain poorly recognized. In general, research pertaining to toxicology and regenerative medicine applications appear to have a better awareness of the necessity for xenofree conditions, likely due to the perceived closer proximity to human application and thus are more closely scrutinized by regulatory bodies to ensure human safety. Our findings show that in order for xeno-free iPSC research standards to be effectively adoptedXenofre it is necessary that well-defined xenofree procedure be developed and standardized by a global non-partisan network of researchers, ethicists, regulators and patient advocate groups. We describe how the creation of an open network along with xenofree resources can address these issues as well as increase the availability of laboratory materials and decrease costs (www.xenofree.org). These resources can thus allow for the pace and accuracy of iPSC research to increase while improving its relevance to human medicine.

Disclosures: **A. Lam:** None. **F. Li:** None. **A.R. Muotri:** None. **E.L. Ohayon:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.30/UU51

Topic: I.02. Systems Biology and Bioinformatics

Support: NSF GRFP

Title: Measuring integrated information in large neural networks

Authors: *D. TOKER[1], F. T. SOMMER[2]
[1]Univ. of California, Berkeley, Berkeley, CA; [2]Univ. California, Helen Wills Neurosci Inst., Helen Wills Neurosci. Inst., Berkeley, CA

Abstract: Brain function is simultaneously parallelized and integrated across specialized regions. While functional specialization in the brain has been extensively studied over the last two centuries, the mechanisms underlying neural information integration remain unresolved. Recently, mathematically principled measures of integrated information have been proposed, which could in principle elucidate the mechanisms of neural information integration, but their extreme computational costs have made them inapplicable to real brain data. We provide a solution to these computational barriers using graph clustering, and reduce the computation time for integrated information in real brain data from longer than the timespan of the universe to just several hours. We estimate integrated information in the brain of *Caenorhabditis elegans*, and find that the structure and dynamics of brains are likely optimized to provide high integrated information.

Disclosures: **D. Toker:** None. **F.T. Sommer:** None.

Poster

174. Systems Biology and Bioinformatics

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 174.31/UU52

Topic: C.01. Brain Wellness and Aging

Support: NIA Grant P30AG050911

Title: Caloric-restriction prevents age-associated epigenetic changes in the old brain

Authors: *N. HADAD[1], D. R. MASSER[2], D. R. STANFORD[2], A. UNNIKRISHNAN[3], A. G. RICHARDSON[3,4], W. M. FREEMAN[2]
[1]Neurosci., [2]Physiol., [3]Geriatrics, The Univ. of Oklahoma Hlth. Sci. Ctr., Oklahoma City, OK; [4]Oklahoma City VA Med. Ctr., Oklahoma City, OK

Abstract: Brain aging is characterized by cognitive decline and increased risk to neurodegenerative disease development. In the CNS, epigenetic mechanisms are vital to proper cellular function and memory formation. Aberrant epigenomic control, specifically in the methylome, is evident with aging and age-related disease. Anti-aging treatments, such as caloric restriction (CR), increase neurogenesis and induce expression of neuroprotective genes in the aged brain. However, the mechanisms underlying these changes remain unknown. In this study, we investigated whether CR, the most proven anti-aging treatment, prevents age-related changes in DNA methylation in the old brain.
To determine the effect of CR on age-related differential methylation in the brain, hippocampal tissue was collected from young (3M) and old (24M) mice fed *ad lib* diet and 24M old mice calorie restricted from 3M to 24M of age. Hippocampal DNA was extracted and used for bisulfite oligonucleotide capture sequencing to determine DNA methylation levels, genome-wide, at a base-specific resolution.
A large number of differentially methylated CpGs (dmCGs) and CpHs were evident with aging, of which 34% and 40% respectively were prevented by CR. CR specific dmCGs were also evident. CH methylation response to diet was different than CGs, where CH hypermethylation with age was 10 times more likely to be prevented by CR than hypomethylation. dmCGs with both age and CR were enriched in CpG island-shelved and gene bodies. Age-related dmCGs unaffected by diet were enriched in H3K4me1 while CR prevented age dmCGs were enriched in H3K27me3. Age-dmCGs affected genes were over-represented in in inflammatory pathways but this was not observed in age-matched CR animals. Genes affected by CR-dmCGs and age-dmCGs, although being different sets of genes, were often co-enriched in similar pathways. Our findings demonstrate for the first time that caloric restriction prevents age-induced changes in DNA methylation in the brain. We also identify a unique effect by CR on CH methylation, emphasizing the importance of investigating both CGs and CHs in aging studies, particularly in the brain. DNA methylation changes induced by CR were also independent of age, suggesting CR may counter-balance the aging process by regulating epigenetic changes that have a protective effect. The prevention of age-dmCGs by CR highlights the prominent role of DNA methylation as a regulator of the aging process.

Disclosures: N. Hadad: None. **D.R. Masser:** None. **D.R. Stanford:** None. **A. Unnikrishnan:** None. **A.G. Richardson:** None. **W.M. Freeman:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.01/UU53

Topic: I.03. Anatomical Methods

Support: 973 projects No. 2015CB7556003

973 projects No. 2015CB75560002.

Title: Chemical sectioning: High throughput brain imaging at axonal resolution

Authors: *S. ZENG[1,2], H. XIONG[1,2], T. YANG[1,2], X. WANG[1,2], Y. GANG[1,2], L. LI[1,2], Q. ZHANG[1,2], Y. LIU[1,2], H. ZHANG[1,2], N. LI[1,2], K. HUANG[1,2], F. YIN[1,2], A. LI[1,2], H. GONG[1,2], Q. LUO[1,2]
[1]Huazhong Univ. of Sci. & Technol., HB, China; [2]MoE Key Lab. for Biomed. Photonics, Dept. of Biomed. Engin., Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: The complex anatomical structures of individual neurons and their synaptic connections form the signal transmission and processing pathway of the nervous system, and therefore are basis for understanding brain functions. However, existing imaging methods cannot cover the huge extension of neurons in mammalian brain with a resolution sufficient to identify connection sites (the pre- and postsynaptic structures). Here we proposed the chemical sectioning (CS) method that enables whole-mouse-brain imaging of genetically defined neuron subset at axonal resolution. For the first time, we show the successful reconstruction of individual neurons extending axonal projections throughout the brain, including all dendrites, centimeter-extended axonal main stems, terminal arborizations, intensive dendritic spines and axonal boutons, and putative synapses. Our method enables quantitative analysis of the morphology, projections, and connectivity of genetically defined neurons. This imaging method will provide a useful tool to examine the integral organization of the brain. Combined with related molecular labeling, this tool pave a new way for neuroscience studies like cell type, neural circuits, and neural computational models.

Disclosures: **S. Zeng:** None. **H. Xiong:** None. **T. Yang:** None. **X. Wang:** None. **Y. Gang:** None. **L. Li:** None. **Q. Zhang:** None. **Y. Liu:** None. **H. Zhang:** None. **N. Li:** None. **K. Huang:** None. **F. Yin:** None. **A. Li:** None. **H. Gong:** None. **Q. Luo:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.02/UU54

Topic: I.03. Anatomical Methods

Title: Generation of the whole brain 3-dimensional atlas for the neuronal diversity with brain-wide precision imaging

Authors: H. GONG[1], *X. LI[1], J. PENG[2], C. ZHANG[3], A. LI[4], J. YUAN[6], Q. LUO[5]
[1]Wuhan Natl. Lab. For Optoelectronics, Hubei, China; [2]Wuhan Natl. Lab. for Optoelectronics-Huazhong Univ. of Sci. and Technol., Wuhan, China; [3]Wuhan Natl. Lab. for Optoelectronics-Huazhong Univ. of Sci. and Technol., wuhan, China; [5]Wuhan Natl. Lab. for Optoelectronics, [4]Huazhong Univ. of Sci. and Technol., Hubei, China; [6]BRITTON CHANCE CENTER FOR BIOMEDICAL PHOTONICS, HUAZHONG UNIVERSITY OF SCIENCE AND TENCHNOLOGY, HUBEI, China

Abstract: Brain has unparalleled cellular diversity that composes local and long distance cortical circuits, and supports complex function. Distinguishing both of basic structural and functional features of different neurons in the brain is still at the center stage in the field. For facilitating classification of neurons on a large scale, we developed a high-throughput precision imaging method that allows us to acquire a co-localized brain-wide dataset of both fluorescent-labeled neurons and counterstained cell bodies at a voxel size of $0.32 \times 0.32 \times 2.0$ μm less than 72 hours for a single mouse brain. Using this method we have acquired mouse whole-brain imaging datasets of cholinergic neurons, corticotropin-releasing hormone (CRH) neurons and somatostatin expressing interneurons (SOM), and then systematically analyzed the distribution of type-specific neurons throughout the whole brain.

Disclosures: H. Gong: None. **X. Li:** None. **J. Peng:** None. **C. Zhang:** None. **A. Li:** None. **J. Yuan:** None. **Q. Luo:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.03/UU55

Topic: I.03. Anatomical Methods

Title: Mouse cerebral vascular atlas in stereotaxic coordinates with one-micron voxel resolution

Authors: *H. GONG, B. XIONG, A. LI, Y. LOU, Q. LUO
Wuhan Natl. Lab. For Optoelectronics, Hubei, China

Abstract: Systematic cellular and vascular configurations are essential for understanding the fundamental brain anatomy and metabolism. Making an ultra-precise atlas for cerebral arteries and veins has been a century-old objective in neuroscience and neuropathology. Using the micro-optical sectioning tomography (MOST) and modified Nissl staining method, we acquired five mouse cerebral vascular datasets with a voxel resolution of one micron. Based on the brain-wide vascular spatial structures and brain regions indicated by cytoarchitecture in one and the same mouse brain, we reconstructed and annotated the fine and complete vascular system atlas of both arteries and veins of the whole mouse brain for the first time. We compared the distributing patterns between the arterial and venous vascular system and brain regions in the whole mouse brain. We also quantitatively analyzed the capillary density in the cortical and subcortical areas of the mouse brain.

Disclosures: H. Gong: None. **B. Xiong:** None. **A. Li:** None. **Y. Lou:** None. **Q. Luo:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.04/UU56

Topic: I.03. Anatomical Methods

Support: 973 Project 2015CB755603

Title: A fast Hematoxylin and Eosin staining of intact tissues

Authors: *Y. LEE[1], N. LI[1], K. HUANG[2], T. ZHENG[3], S. ZENG[1], X. LIU[1]
[1]Britton Chance Ctr. for Biomed. Photonics, Huazhong Univ. of Sci. and Technol., Hubei, China; [2]Convergence Technol. Co., Ltd., Wuhan, China; [3]Wuhan OE-Bio Co., Ltd, Wuhan, China

Abstract: Hematoxylin and Eosin (H&E) staining, a traditional method to obtain the morphology information of biological tissues, has been widely used in biomedicine field, including pathologic diagnosis in the hospital. In H&E staining procedure, hematoxylin is used to stain the cell nucleuses to make them mazarine. Meanwhile, the cytoplasm and extracellular matrix will be stained to pink with different color level. Generally, the sample is cut into slices of 2 ~ 7 μm thickness for uniform staining, as large tissue blocks or intact tissues cannot be stained uniformly.The development of whole-mount imaging techniques, such as micro-optical sectioning tomography system, helps to obtain three-dimension imaging of whole-mount tissues

labeled with dyes or fluorescent proteins. However, imaging a whole-mount H&E stained sample is still difficult due to the inhomogeneous H&E labeling in a large-volume tissue.Here we introduce a novel method to achieve fast and uniform H&E staining. By using dichloromethane to delipid and other physical and chemical modulations in the labeling procedures, we can stain large-volume tissue blocks like intact mouse brains fast and uniformly.

Disclosures: **Y. Lee:** None. **N. Li:** None. **K. Huang:** None. **T. Zheng:** None. **S. Zeng:** None. **X. Liu:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.05/UU57

Topic: I.03. Anatomical Methods

Title: A three-dimensional image registration method for brain-wide positioning system

Authors: *H. NI, Z. FENG, C. TAN, S. CHEN, H. GONG, Q. LUO, A. LI
Wuhan Natl. Lab. For Optoelectronics, Hubei, China

Abstract: The accurate neural structures and precise brain spatial localization is crucial for analyzing the structure and function of brain circuits. The latest brain-wide positioning system (BPS) achieved the high-throughput dual-color precision imaging, which offered an opportunity to brain circuit deconstruction with provided co-localized fluorescent-labelled neurons and counterstained cytoarchitectural data sets in the whole brain. However, a direct mapping of original date sets to the reference atlas is impossible because of the morphological differences between different individuals and the data sets are easily-interfered during image acquisition. As an extension of BPS technology we proposed a Seg-Reg Co-registration pipeline which mapped 3D brain imaging data sets to reference atlas and then enabled the precise positioning of neural circuits. Compared with traditional methods,this pipeline introduced a slightly time-consuming semi-automatic segmentation and an up-sampling displacement strategy for ensuring a rapid, accurate, generic and easily-controlled 3D nonlinear registration of mouse brain imaging date sets. In summary, our co-registration pipeline established an effective solution for 3D spatial localization of whole-brain studies such as neuronal projection, gene expression and the Brain Connectivity Atlas.

Disclosures: **H. Ni:** None. **Z. Feng:** None. **C. Tan:** None. **S. Chen:** None. **H. Gong:** None. **Q. Luo:** None. **A. Li:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.06/UU58

Topic: I.03. Anatomical Methods

Title: Acquiring golgi-stained neuronal morphology with co-located cytoarchitecture in the same mouse brain

Authors: *X. CHEN, X. ZHANG, Q. ZHONG, Q. SUN, J. PENG, H. GONG, J. YUAN
Wuhan Natl. Lab. For Optoelectronics, Wuhan City, China

Abstract: Acquiring accurate orientation reference is prerequisite to precisely analyzing the Golgi-stained neural morphology in whole brain. However, there is no method to simultaneously acquire cytoarchitecture for Golgi-stained neurons in the whole brain. Here, we developed a Dual-mode Micro-Optical Sectioning Tomography (dMOST) method, to simultaneously acquire Golgi-stained neural morphology and fluorescence-labeled anatomic reference in the same brain. Combining real-time counterstaining during data acquisition, this method allowed us to simultaneously detect both reflective (for Golgi staining) and fluorescent (for cytoarchitecture staining) signals. We acquired a full-volume, dual-color mouse brain dataset of Golgi-stained neurons with co-located cytoarchitecture at a voxel size of $0.32 \times 0.32 \times 1.0$ μm in 4 days. We also acquired and analyzed the Golgi-stained neural morphological features at single-neuron resolution in specific brain regions for pathological and physiological models. We believe that our method would facilitate the study on the structural principle of brain function and disease.

Disclosures: X. Chen: None. **X. Zhang:** None. **Q. Zhong:** None. **Q. Sun:** None. **J. Peng:** None. **H. Gong:** None. **J. Yuan:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

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Program#/Poster#: 175.07/UU59

Topic: I.03. Anatomical Methods

Support: National Natural Science Foundation of China Grant 31571002

Science Fund for Creative Research Group of China Grant 61421064

Seed project of Wuhan National Laboratory for Optoelectronics

Optical Bioimaging Core Facility of WNLO-HUST

Title: Skull optical clearing window for *In vivo* imaging of the cortex in mice

Authors: *Y. ZHAO[1,2], C. ZHANG[1,2], Z. LI[1,2], T. YU[1,2], T. XU[1,2], D. ZHU[1,2]
[1]Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol., Hubei, China; [2]Key Lab. for Biomed. Photonics of Ministry of Educ., Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: Combined with transgenic technology, two-photon laser scanning microscopy has made it possible to understand a broad range of neurobiological phenomena in the living brain. However, the skull over the cortex presents strong scattering effects, and thus various cranial window techniques were developed to improve the imaging performance, including the open-skull glass window, thinned-skull cranial window, and their variants. However, these methods present limitations: it may cause a significant inflammatory response within three weeks after surgery or it is quite difficult to carry out especially when imaging the fine structure of neurons. In this work, we developed an easy-handling skull optical clearing window (SOCW) without craniotomy, which allowed us to repeatedly image the fine neuronal structures in the superficial layers of the neocortex. In addition, the microglia, astrocytes and vascular data collectively showed that this method did not induce classic inflammatory response in the brain. Then we applied this method to study the postsynaptic dendritic spine plasticity in the critical period, and to monitor the dynamics in dendrites and microglia after two-photon laser ablation. Given its safety and excellent performance, this technique holds great promise for its application in neuroscience research.

Disclosures: **Y. Zhao:** None. **C. Zhang:** None. **Z. Li:** None. **T. Yu:** None. **T. Xu:** None. **D. Zhu:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.08/UU60

Topic: I.03. Anatomical Methods

Title: Brainsmatics—Bridging the brain science and brain-inspired artificial intelligence

Authors: *Q. LUO
Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol., Hubei, China

Abstract: We propose a new approach of brain-spatial information science, abbreviated to brainsmatics, which refers to the integrated, systematic approach of tracing, measuring, analyzing, managing and displaying cross-level brain spatial data with multi-scale resolution. We discussed its research contents, technological systems and key scientific problems, analyzed its discipline orientation, and forecasted the applications. Taking the Micro-Optical Sectioning Tomography (MOST) serial techniques as the core, we have developed a multidisciplinary complete technical system of Visible Brain-wide Network (VBN), which makes brainsmatics more mature. Based on big data of three-dimensional fine structural and functional imaging of neuron types, neural circuits and networks, vascular network et al, with definite temporal-spatial resolution and specific spatial locations, brainsmatics makes it possible to better decipher the brain function and disease and promote the brain-inspired artificial intelligence by extracting cross-level and multi-scale temporal-spatial characteristics of brain connectivity.

Disclosures: Q. Luo: None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.09/UU61

Topic: I.03. Anatomical Methods

Title: High-throughput strip-scanning fluorescence micro-optical sectioning tomography with improved optical sectioning

Authors: *Q. ZHONG, J. YUAN, Y. HAN, C. ZHOU, X. LV, H. GONG, Q. LUO
Wuhan Natl. Lab. For Optoelectronics, Hubei, China

Abstract: Whole-brain optical imaging technologies open a door to decipher brain structure with single-neuron resolution. However, data acquisition time of several days for a whole mouse brain limits these technologies to achieve large-scale industrialized data acquisition for brain connectome and projectome. Here, we propose a strip-scanning fluorescence micro-optical sectioning tomography (fMOST) to improve high throughput and accelerate data acquisition of whole-brain optical imaging. We employed strip scanning to rapidly cover the entire imaging range of single coronal plane. We used a novel structured-illumination imaging to achieve optical sectioning without multiple illumination modulation. The image of a 100 μm-thick *Thy*1-GFP M-line transgenic mouse brain slice demonstrates the effective background inhibition of our method. We imaged a mouse brain coronal slice of 10 × 6.5 mm at a xy resolution of 0.16 × 0.16 μm in about 125 seconds. It demonstrates a 2.6× improvement of imaging throughput of single coronal plane, comparing with previous whole-brain imaging method. Our method potentially becomes a routine tool for anatomical data acquisition of neuroscience.

Disclosures: **Q. Zhong:** None. **J. Yuan:** None. **Y. Han:** None. **C. Zhou:** None. **X. Lv:** None. **H. Gong:** None. **Q. Luo:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.10/UU62

Topic: I.03. Anatomical Methods

Support: 973 Project 2015CB755603

Title: Whole mount *In situ* hybridization of mouse brain to precisely locate mRNAs via fluorescence tomography

Authors: *W. GUO, Y. GANG, F. YIN, P. LI, F. HUANG, N. LI, Q. ZHANG, Y. LI, Y. JIA, F. XIONG, X. WANG, X. LIU, H. GONG, Q. LUO, S. ZENG
Wuhan Natl. Lab. for Optoelectronics, Huazhong Univ. of Sci. and Technol., Hu Bei, China

Abstract: Introduction Rich biological information involves in the nucleic acids of intact biological tissues. Whole mount in situ hybridization is a powerful technique to mine the wealth of DNAs or RNAs, especially mRNAs. However, there are no simple, rapid approaches to exactly locate mRNAs in large tissues such as intact brains. Combining the penetration procedures of iDISCO with the signal amplification approach termed hybridization chain reaction, here we developed a method for whole brain in situ hybridization at cellular resolution. Based on fluorescence tomography instead of tissue clearing, this method provides a simple, rapid way to precisely locate mRNAs in the whole brain with cytoarchitectonic landmarks. We demonstrated to investigate the exact distributions of Cre mRNAs in the Thy1-cre mouse brain, and found there were high levels Cre mRNA in most regions of the subcortical nuclei and the brain stem but comparatively low levels in major areas of the cerebral cortex.
Methods In the current research on mRNAs of the intact mouse brain, with the help of penetration skills in iDISCO and a signal amplifying technique termed hybridization chain reaction(HCR), we developed a simple, rapid method to precisely locate mRNAs of intact mouse brain at cellular resolution via whole mount in situ hybridization and fluorescence tomography. The first three steps included the brain obtaining via heart perfusion, the whole mount FISH via hybridization chain reaction (HCR) and the resin embedding by HM20. The last three steps are imaging cycles of the PI real-time counterstaining, the wide field imaging and the tissue block surface removing. The cutting and imaging depth is 1~2 μm and can reach submicron level when needed. During the processes of fluorescence tomography, the constantly produced two dimensional images could be registered into 3D images automatically and real-timely. From sample obtaining to imaging acquisition, the total time took about 2 weeks(13~15 days). And the fluorescence in situ hybridization via hybridization chain reaction took only 2 days, which was

much more rapid than the whole mount immunohistochemistry (IHC).
Results
Conclusions A simple, rapid method for whole mount fluorescence mRNA in situ hybridization of the intact mouse brain was developed. Using this method, the precise spatial distribution patterns of mRNAs inside the whole mouse brain at cellular resolution could be acquired within about two weeks.

Disclosures: W. Guo: None. **Y. Gang:** None. **F. Yin:** None. **P. Li:** None. **F. Huang:** None. **N. Li:** None. **Q. Zhang:** None. **Y. Li:** None. **Y. Jia:** None. **F. Xiong:** None. **X. Wang:** None. **X. Liu:** None. **H. Gong:** None. **Q. Luo:** None. **S. Zeng:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.11/DP14/UU63 (Dynamic Poster)

Topic: I.03. Anatomical Methods

Support: 973 project No. 2015CB7556003

NSFC No. 81327802

NSFC No. 61421064

WNLO director funds

Title: Advanced NeuroGPS-Tree achieves brain-wide reconstruction of neuronal population equal to manual reconstruction level

Authors: *Q. TINGWEI[1,2], H. ZHOU[1,2], S. LI[1,2], L. LI[1,2], Y. GANG[1,2], Q. LUO[1,2], H. GONG[1,2], S. ZENG[1,2], A. LI[1,2]
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Abstract: The brain-wide reconstruction of neuronal population is an indispensible step towards exploring the complete structure of neuronal circuits, a central task that underlies the structure-function relation in neuroscience. Recent advances in molecular labeling and imaging techniques enable us to collect the whole mouse brain imaging dataset at cellular resolution, including the morphological information of neurons across different brain region or even the whole brain. Reconstruction of these neurons poses substantial challenges, and at presents there is no tool for high-speed achieving this reconstruction close to human performance. Here, we presented a tool for filling in the blanks. The tool mainly contains the following function modules: 3D

visualization of large-scale imaging dataset, automated reconstruction of neurons, manual editing of the reconstructions at local and global scale. In this tool, in the framework of our previous tools (NeuroGPS-Tree and SparseTracer), the two identifying models were constructed for boosting the automatic level of the reconstruction. One is used to identify the weak signals from inhomogeneous backgrounds and the other is used to identify closely packed neurites. This tool can be suitable for the different big-data formats like MOSTd and Terafly, and can make the dataset be fastly read into memory for the reconstruction. The manual editing module in this tool can correct the errors drawn from above automated algorithms. And thus helps to achieve the reconstruction closer to human performance. We demonstrated the features of our tool on various kinds of sparsely labelled datasets. The results indicated that without loss of the reconstruction accuracy, our tool has a 7-10 folds speed gain over the commercial software that provides the manual reconstruction.

Disclosures: **Q. Tingwei:** None. **H. Zhou:** None. **S. Li:** None. **L. Li:** None. **Y. Gang:** None. **Q. Luo:** None. **H. Gong:** None. **S. Zeng:** None. **A. Li:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.12/UU64

Topic: I.03. Anatomical Methods

Title: A platform for efficient identification of molecular phenotypes of brain-wide neural circuits

Authors: *J. YUAN, H. GONG, T. JIANG, B. LONG, T. XU, Q. LUO
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Abstract: Molecular phenotyping neural circuits are crucial to elucidating the operating mechanisms of brain function. However, no efficient, systematic approach is available for describing the molecular features of specific neural circuits at the whole brain scale. Here, we propose an efficient approach to map brain-wide structural and molecular information in the same brain: rapidly imaging and sectioning the whole brain as well as automatically collecting all slices; conveniently selecting slices of interest through quick data browsing and then performing post hoc immunostaining of selected slices. To this aim, we developed a rapid whole-brain optical tomography method to image the whole brain and collect all slices. Using this platform, we mapped the brain-wide distribution of inputs to motor, sensory and visual cortices and identified their molecular phenotypes in several subcortical regions. Together with its high efficiency, our platform provides access to automation and industrialization of cell type analyses for specific circuits.

Disclosures: **J. Yuan:** None. **H. Gong:** None. **T. Jiang:** None. **B. Long:** None. **T. Xu:** None. **Q. Luo:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

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Support: National Natural Science Foundation of China Grant 31571002

Science Fund for Creative Research Group of China Grant 61421064

Seed project of Wuhan National Laboratory for Optoelectronics

Optical Bioimaging Core Facility of WNLO-HUST

Title: Optimization of 3DISCO for whole-brain clearing and imaging

Authors: ***T. YU**[1,2], Y. QI[1,2], J. XU[1,2], Y. LI[1,2], H. GONG[1,2], Q. LUO[1,2], D. ZHU[1,2]
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Abstract: Various optical clearing methods have emerged as powerful tools for three-dimensional imaging and reconstruction of the structures deep in biological tissues. Thereinto, 3DSICO, as an organic-solvent-based clearing method, could achieve the highest level of tissue transparency and substantial volumetric reduction, which were advantageous for imaging larger volumes compared with other aqueous-solution-based clearing methods. 3DISCO has been used to study various tissues and be combined with whole-mount immunolabeling for facile volume imaging of structures in complex tissues, including brain. However, 3DISCO results in fast decline of endogenous fluorescent signal during the clearing procedure, and it has a rather short storage time limited to approximately 1-2 days, which has impeded the application of 3DISCO especially on large samples, such as whole brain. To overcome this, uDISCO has been developed to preserve the fluorescence better and maintain it over weeks to months. In this study, we proposed a modified method based on 3DISCO for better fluorescence preservation and longer storage time, termed as mDISCO (modified 3DISCO), to provide an alternative clearing method for the researchers. We investigated the influence of mDISCO on signal preservation of different fluorescent proteins, such as green fluorescent protein (GFP), yellow fluorescent protein (YFP) and tdTomato fluorescent protein. Simultaneously, we evaluated the performance of mDISCO in other aspects, including tissue transparency, size change of samples, morphology maintenance, and the compatibility with diverse fluorescent probes. All these factors were compared with the

original 3DISCO. The results demonstrated that the mDISCO could obtain 2-4 folds increase in signal intensity of endogenous fluorescent proteins and achieve longer storage time up to weeks by retaining the advantages of original protocol. By using mDISCO, we cleared and imaged the entire adult mouse brain, and reconstructed the neuronal projections in single-cell resolution. In a word, mDISCO could achieve better fluorescence preservation than 3DISCO, and demonstrated similar capability with uDISCO. This optimized method could provide an alternative method for researchers, broaden the applicability of 3DISCO, and make it potentially suitable for weak fluorophores. What's more, this modification protocol might also be applicable to other solvent-based clearing methods.

Disclosures: **T. Yu:** None. **Y. Qi:** None. **J. Xu:** None. **Y. Li:** None. **H. Gong:** None. **Q. Luo:** None. **D. Zhu:** None.

Poster

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Topic: I.03. Anatomical Methods

Support: the National Natural Science Foundation of China (Grant No. 31270906, 31470056)

the Director Fund of the Wuhan National Laboratory for Optoelectronics

Title: Sparse and high-bright neuronal labeling for brain-wide reconstructing complete morphologies of individual neurons in mice

Authors: *Z. YU-HUI[1], P. SUN[1], S. JIN[2], X. HE[2], J. KUANG[1], Y. GANG[1], H. LIN[1], Q. LUO[1], H. GONG[1], S. ZENG[1], F. XU[2], J. PENG[1]
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Abstract: How to efficiently and conveniently label various neurons in different brain regions not only with extreme sparseness but also with high brightness in neuronal branches is still challenging and a fundamental requirement in drawing out the integral morphologies of individual neurons in mice. We developed a novel efficient and convenient method that can label various neurons in different brain regions not only with extreme sparseness but also with extreme high brightness in neuronal arbors in mice. We used a special engineered adeno-associated virus AAV-EF1α-double floxed-EYFP (Mix) alone to label 20-150 neurons in different brain regions in C57 mice with axonal projections brightly enough to be traced throughout a whole mouse brain. Based on our labeling method and a whole-brain imaging system (TDI-fMOST), we

successfully traced and reconstructed uninterrupted three-dimensional (3D) complete morphologies of 30 neurons in lateral prefrontal cortex (LPFC). Our results represent a general convenient, sparse, and bright labeling strategy for reconstructing the integral morphologies of individual neurons in a whole mouse brain.

Disclosures: **Z. Yu-Hui:** None. **P. Sun:** None. **S. Jin:** None. **X. He:** None. **J. Kuang:** None. **Y. Gang:** None. **H. Lin:** None. **Q. Luo:** None. **H. Gong:** None. **S. Zeng:** None. **F. Xu:** None. **J. Peng:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

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National Natural Science Foundation of China Grant 31571002

Science Fund for Creative Research Group of China Grant 61421064

Title: Bessel Brain-wide light-sheet fluorescence microscopy (2B-LSFM) for high-resolution, isotropic imaging of ultra-fine neural structures

Authors: T. YU[1], X. WANG[2], Y. LI[1], C. FANG[2], *D. ZHU[1], P. FEI[2]
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Abstract: Study of the brain is the hottest topic in neuron science. The complex functionalities of brain is highly from its complicated neuron structures (circuits). For better understanding how the brain works, it is crucial to map the neuron network at whole brain level, with high resolution. Among a variety of optical brain imaging techniques, such as serial two photon tomography (STP), micro-optical sectioning tomography (MOST), light-sheet fluorescent microscopy (LSFM) has recently emerged for its advantages of high-throughput and low photo-bleaching. However, compared to STP or MOST, its relatively low axial resolution at whole-brain scale limits its application for visualizing the neural connections in the brain, at subcellular level. We hereby develop a Bessel brain-wide light-sheet fluorescence microscopy (2B-LSFM) for high-resolution, isotropic imaging of ultra-fine neural structures. Merely using continuous wave laser combined with large apex axicon, large aperture lenses, and tightly-synchronized

confocal slit of camera, we final realize superior scanning Bessel light-sheet illumination on whole mouse brain, with 2 cm-long working distance, 2 mm-wide coverage and only 1 μm-sharp excitation at the vicinity of the focal plane. Using 2B-LSFM, we obtain the 3-D connections of the giant pyramidal neurons in a whole mouse brain, including their tip dendrites and long axon projections, with an isotropic voxel resolution of 0.5 by 0.5 by 0.5 μm. Compared to the hyperbolic Gaussian laser-sheet which is the mainstream of LSFM, our 2B method improves the axial resolution of current LSFM-based whole brain imaging for 5 to 10 folds. By a relatively cost-effective means, with keeping the high-throughput, low photon burden advantages, 2B-LSFM method further achieves subcellular, isotropic resolution at whole-brain scale. Thus it shows great potentials for various applications of neuron/brain research.

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Poster

175. Connectomics: Automatic Tracing Techniques

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Support: 973 project No. 2015CB7556003

NSFC No. 81327802

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WNLO director funds

Title: Identifying weak signals in inhomogeneous neuronal images for large-scale tracing of neurites

Authors: *S. LI[1,2], T. QUAN[1,2], F. YIN[1,2], R. GUO[1,2], H. ZHOU[1,2], A. LI[1,2], L. FU[1,2], Q. LUO[1,2], H. GONG[1,2], S. ZENG[1,2]
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Abstract: Reconstruction the neuronal morphology across different regions or even the whole brain is important for many neuroscience research topics. Large-scale tracing of neurites constitutes the core part of this kind of reconstruction, and faces many challenges. The key one is to identify quite weak signal from the inhomogeneous background. Here, we addressed this problem by constructing the identifying model. In the construction, the empirical observations on

neuronal images are summarized into the rules, the rules are used to design feature vectors that display the differences between the foreground and background, and support vector machine is used to learn these feature vectors. We embedded the identifying model into our previous tool, SparseTracer, named SparseTracer-Learned Feature Vector (ST-LFV). ST-LFV can trace the neurites with extremely weak signals (SBR<1.1) from inhomogeneous ground. By testing 12 sub-blocks extracted from the whole imaging dataset, ST-LFV can achieve the average recall rate of 0.99 and precision rate of 0.97, superior to SparseTracer (average recall rate 0.93 and precision rate 0.86), a well suited method of weak signal identification. We applied ST-LFV in tracing neurites from large-scale images (about 105 GB). In the tracing process, obtaining the results equal to the gold standard required only one manual editing for ST-LFV, versus 20 times manual editings for SparseTracer. The improvement of the automatic reconstruction level indicates that ST-LFV has the potential to quickly reconstruct the sparsely-distributed neurons at the whole brain scale.

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Poster

175. Connectomics: Automatic Tracing Techniques

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Topic: I.03. Anatomical Methods

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Title: DeepBouton: Automated identification of single-neuron axonal bouton in the whole brain

Authors: ***S. CHENG**, T. QUAN, X. WANG, Y. LIU, X. LIU, H. GONG, S. ZENG, Q. LUO
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Abstract: Axonal boutons are typical presynaptic structures and represent destination sites of the transported neural information. The localization of boutons in a single neuron is important for understanding neural circuits. Recently developed labeling and imaging techniques have enabled us to obtain submicron-resolution whole brain dataset, which provides detailed structure of a single neuron including axonal boutons. However, identifying the boutons poses substantial challenges: varying radius and signal intensity of axons generating false bouton patterns, diversities of bouton size and intensity, huge image datasets. Here, we proposed an automatic method for single-neuron bouton identification in whole brain using density-peak clustering and

deep convolutional neural networks. The presented method adopted two-step recognition strategy: density-peak clustering to detect underlying bouton centers and deep convolutional networks for filtering false positives in initially detected boutons. The method combined the robustness of density peak clustering segmenting objects with various patterns and the adaptive feature representation ability of deep learning models, and can effectively detect boutons of various morphologies and overcome the disturbance of axon signal variation. In addition, we developed bouton sample simulation to reduce massive man labor of annotating training samples. To validate our method, we applied it to identify the boutons of a pyramidal cell in M1 layer 5 region, distributed in a $3.0 \times 6.2 \times 3.1$ mm^3 volume. 21587 boutons were detected with an F_1-measure of 0.89. We also applied it to other types of cells, and the previous learned network could be easily transferred and finetuned with a small number of samples. To our knowledge, this method is the first attempt to identify single-neuron axonal boutons in the whole brain.
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Poster

175. Connectomics: Automatic Tracing Techniques

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Science Fund for Creative Research Group of China Grant 61421064

Seed project of Wuhan National Laboratory for Optoelectronics

Optical Bioimaging Core Facility of WNLO-HUST

Title: A large-scale, switchable optical clearing skull window for cerebrovascular imaging

Authors: *C. ZHANG[1,2], Y. ZHAO[1,2], W. FENG[1,2], R. SHI[1,2], T. YU[1,2], T. XU[1,2], P. LI[1,2], Q. LUO[1,2], D. ZHU[1,2]
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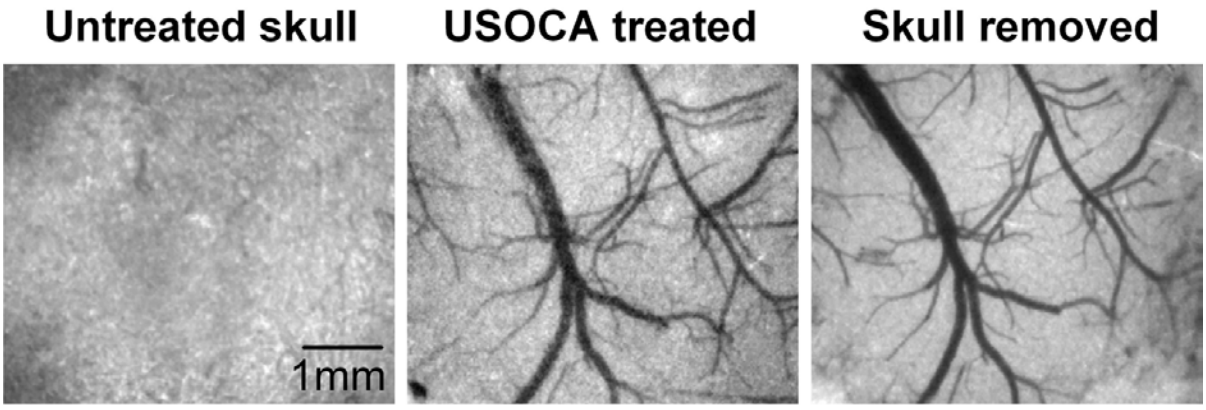
Abstract: *In vivo* optical imaging of cortex is of great important for revealing both structural and functional architecture of brain. However, the high scattering of skull limits optical imaging qualities. To resolve this problem, skull optical clearing agent (U-SOCA) is developed for

establishing an optical clearing skull window, which permits to image through intact skull to improve imaging qualities, without limitation of imaging modalities. Optical clearing skull window is efficient for mice at different age stage, and image quality through this skull window is nearly comparable to that of removing skull. Besides, U-SOCA is also competent for short-term or long-term investigations, at the same time, it nearly would not cause changes in cerebral hemodynamics and has no influence on cerebrovascular structure. Except that, U-SOCA is useful for wide-field clearing and imaging through intact skull as well, permitting to choose an ideal region of interest (ROI) for investigation and monitor dynamic changes of the whole cortex during a brain disease process, such as stroke. Additionally, the safety of USOCA has also been evaluated from several aspects, including exploring the activation of microglia cells, expression of glial fibrillary acid protein (GFAP), as well as metabolic toxicity, and the results indicated that this skull optical clearing window almost had no influence on stabilization of brain homeostasis, and USOCA does not have influences on mice growth and induce abnormal changes in organs, implying that USOCA was free of metabolic toxicity.In summary, this method features a convenient, switchable, size-adjustable and safe skull window for *in vivo* optical imaging, promising to be applied to monitor dynamic changes in physiological and pathological processes.The optical clearing efficiency is shown as follows (White light images of cerebral vessels on condition of untreated skull, USOCA treated skull and removing skull, respectively).



Disclosures: **C. Zhang:** None. **Y. Zhao:** None. **W. Feng:** None. **R. Shi:** None. **T. Yu:** None. **T. Xu:** None. **P. Li:** None. **Q. luo:** None. **D. Zhu:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

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Support: KIST Joint Research Lab

National Research Foundation of Korea (Grant No. 2016R1C1B2007319, 2016R1A4A1010796)

Korea Health Industry Development Institute (Grant No. HI15C2887)

Title: Volumetric mGRASP: Large-scale 3D mapping of mammalian synaptic connectivity with light microscopy

Authors: *S.-Y. KIM[1], D.-J. KOO[1], H. LEE[2], H.-E. PARK[1], J. KIM[3]
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Abstract: Complete mapping of neural connectivity (the connectome) across the mammalian brain is a daunting and exciting prospect. Achieving this goal requires three-dimensional, high-resolution reconstruction of all neurons and their fibers and determining the exact location of synapses throughout the whole brain. With relevance for this goal, various clearing and labeling techniques for large-scale tissues have been developed, including CLARITY, CUBIC, and SeeDB. These techniques, using different principles, render the tissue samples sufficiently transparent for imaging fluorescently labeled cell bodies and fibers millimeters deep into the brain tissue. Visualization of some dendritic spines and synaptic proteins were also demonstrated using some of these techniques. However, precise detection and visualization of specific synapses between defined subpopulations of neurons in the cleared, large-scale tissue volume remain an unmet goal.

We considered that the mGRASP technique (mammalian GFP reconstitution across synaptic partners) might allow us to achieve the precise detection and visualization of synapses in the cleared tissue volume. mGRASP enables bright fluorescent labeling of the synapses between two defined neural subpopulations, based on proximity-dependent functional complementation between two non-fluorescent GFP fragments at the synaptic cleft. Consequently, mGRASP enables precise detection of nanometer-scale synapses with diffraction-limited microscopy methods. Due to the light scattering from the conventional tissue preparations during image acquisition, however, the application of mGRASP has been limited to ~100-um thick sections at maximum. Such limitations in imaging depth are now addressable with newly developed tissue clearing techniques. Therefore, tissue clearing techniques and mGRASP synergistically complement each other for the visualization of defined synapses across millimeter-scale tissue volume.

Here we applied the latest versions of three aqueous-based tissue clearing techniques—passive CLARITY, CUBIC, and SeeDB2—and compared their performance in clearing and visualization of mGRASP signals through the tissue volume. We sought to optimize each technique to obtain the best possible results, and our preliminary data indicate that modified CLARITY and CUBIC protocols yield the best clearing performance without significantly compromising genetically expressed mGRASP signals. We are currently working on further optimization of each technique, and are also applying our “volumetric mGRASP” technique to several brain circuits to understand their precise circuit organizations.

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Poster

175. Connectomics: Automatic Tracing Techniques

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Title: Molecular and electrophysiological interaction between heart and sensory neurons

Authors: *T. AKGUL, M. Y. GUNAL, G. OZTURK, E. CAGAVI
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Abstract: Inputs from nervous system through sympathetic and parasympathetic neurons are critical to regulate heart function. As important is the sensory output from heart to brain, as previously described at the level of pain and pressure. Even though the motor control of autonomic nerves over the heart is well characterized in the literature; the variety of sensory information, the molecular mechanism, level and components of the interaction between the sensory neurons and the heart is largely unknown. To this end, the main aim of this study is to understand the cellular, molecular and electrophysiological mechanism between myocardium and the innervating sensory neurons specific to the heart. It is known that, the sensory neurons transmit signals regarding the homeostatic condition of the heart to the brain via dorsal root ganglion (DRG) and Nodose ganglion (NG). In this study, we have primarily investigated the interaction by co-culturing mouse cardiomyocytes and DRG or NG neurons by immune staining and SEM imaging. In our cocultures, we have observed an axon based physical interaction between DRG neurons and cardiomyocytes evident with SEM analysis. In order to explore the relevance of this interaction in vivo, we have injected an axonal retrograde dye to the heart of adult mice and collected DRG and NG to trace cardiac-specific sensory neurons. After 1, 3, 7, 14 days of injection, NG and DRG located in cervical and thoracic levels were dissociated enzymatically and observed under the confocal microscope. As our retrograde dye is fluorescent and voltage-sensitive, the fluorescently-labeled cardiac specific neurons were observed both at the level of tissue and dissociated cell cultures. In addition, optogenetic tools were used to investigate the direction of electrical signal and molecular mechanism between cardiomyocytes and interacting sensory neurons. Membrane potential of cardiomyocytes and neurons infected with channel rhodopsin 2 (ChR2) coding adenovirus were controlled with blue light. Our findings suggest that, cardiomyocytes respond to ChR2 stimulation. Prolonged stimulation with blue light showed attenuation of spontaneous beating of cardiomyocytes. In the following experiments, we plan to FACS purify *in vivo* labeled cardiac-specific sensory neurons and

coculture with cardiomyocytes to investigate the molecular interaction by epigenetic analysis, qRTPCR and immunocytochemistry methods. The findings from this study will shed light into cellular and molecular basis of heart and sensory nervous system interaction.
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Poster

175. Connectomics: Automatic Tracing Techniques

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Topic: I.03. Anatomical Methods

Support: CIHR 39090-59420

CIHR 39654-59420

Title: Increase in dendritic spine numbers revealed using Dii in *In vitro* slices

Authors: *J. S. TRIVINO PAREDES[1], P. C. NAHIRNEY[1,2,3], B. R. CHRISTIE[1,3,4]
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Abstract: The hippocampus is a key brain structure involved in learning and memory that is widely used for studying synaptic plasticity both in vitro and in vivo. Over the years a number of different approaches have been developed to optimize slice viability and increase the reproducibility of recordings during these procedures. Careful attention has been given to several different variables, including the age of the animal, composition of the artificial cerebrospinal fluid (aCSF), temperature and slice-cutting methodology. Recently, both electron microscopy and two-photon microscopy approaches have been used to show that dendritic spine numbers can be significantly altered in vitro, and that cells in these preparations routinely have more dendritic spines than are normally observed in cells from perfusion-fixed hippocampi. This is a concern as alterations in dendritic spines could impact a number of cellular processes related to synaptic plasticity and create discrepancies between in vitro and in vivo electrophysiological studies. Because the juvenile brain is in a period of intense synaptic change, we are particularly interested in how in vitro slice preparation affects spine numbers in these animals. We compared dendritic spine density in the cornu ammonis 1 and dentate gyrus between acute slices prepared for in vitro use (i.e. in aCSF) and those in perfusion-fixed brains of young male and female Sprague-Dawley rats. Dendritic spines were visualized by staining the cell bodies with the lipophilic carbocyanine

dye, DiI (1,1'-Dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate). In support of previous studies, we observed that preparing slices for in vitro use increased dendritic spine density. Future studies will focus on the impact of other variables on dendritic spines and possible influences on synaptic plasticity processes.

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Poster

175. Connectomics: Automatic Tracing Techniques

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Title: Automatic reconstruction of vessels in images from cleared specimens

Authors: *S. TAPPAN, A. RODRIGUEZ, M. A. KARIM, D. HOPPES, C. THOMAS, P. J. ANGSTMAN, J. R. GLASER
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Abstract: Decades of research indicate a critical role of the microvasculature in the plasticity of the brain under various physiological and pathological conditions (e.g., TBI, stroke). The advent of tissue clearing techniques offers the opportunity to investigate these processes in previously unavailable extent and detail. In the current study, we demonstrate the utility of cleared tissue image volumes and the functionality of specialized quantitative software for the study of microvasculature.
uDISCO, CLARITY and other related tissue clearing agents have enabled unprecedented studies of neuroanatomy and cytoarchitecture by removing the necessity of tissue sectioning. As imaging methodologies evolve for these intact specimens, it is also evident that specialized quantitative tools need to be developed. Cleared specimens are often millimeters thick and successful imaging requires sophisticated and expensive microscopy equipment (e.g., lightsheet microscopy and super long working distance objective lenses). The resulting uncompressed image data can be very large (>0.5 TB). As such, developing technologies for analyzing image data from intact cleared specimens presents special challenges in image access, viewing, and processing.
Computationally efficient methods for viewing and tracing this class of big data are a central necessity. To meet these needs, we first created three algorithms that are each capable of reconstructing the entire intact volume in fully automatic mode. Additionally, these algorithms can be used together in user-guided tracing for accommodating the variation in image quality or labeling density in different regions of the brain. In large volumes, the complexity of the

resulting data models of the vessel networks is too dense to evaluate as a whole. To overcome this challenge, Vesselucida provides data models that are optimized for efficient display of the entirety or a focused region of interest for robust interaction and correction.
To validate our automatic tracing technologies, models were compared before and after correction using a full suite of integrated tools for visualization, manual reconstruction, and editing to characterize types of errors generated automatically. This was used to iteratively refine the performance of the automated algorithms. In conclusion, these newly developed reconstruction methods provide reproducible, validated models to examine the microvasculature network organization in the brain.

Disclosures: **S. Tappan:** A. Employment/Salary (full or part-time):; MBF Bioscience. **A. Rodriguez:** A. Employment/Salary (full or part-time):; MBF Bioscience. **M.A. Karim:** A. Employment/Salary (full or part-time):; MBF Bioscience. **D. Hoppes:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C. Thomas:** A. Employment/Salary (full or part-time):; MBF Bioscience. **P.J. Angstman:** A. Employment/Salary (full or part-time):; MBF Bioscience. 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.; R44MH099731. **J.R. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience.

Poster

175. Connectomics: Automatic Tracing Techniques

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 175.23/UU75

Topic: I.03. Anatomical Methods

Support: UNIST Grant 1.170009.01

Title: Quantitative analysis and prediction of neuronal response via one-photon photolysis of caged glutamate

Authors: *H. YANG[1], J. LEE[2], G. CHOI[2], W.-G. JUNG[2], C.-M. GHIM[1,2]
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Abstract: Neural stimulation from uncaged neurotransmitters via photolysis has been widely used for discoveries in neuroscience. Despite its widespread use, the understanding of the photo-release and the ensuing neural response remains largely qualitative. Here, we built an analytical framework to describe a series of random processes from the photo-release of caged glutamate to the reaction and diffusion thereof as a function of the quantitative attributes of the light source. In our modeling scheme, neural stimulation by photolytic uncaging of neurotransmitters is

broken down into four stages: 1) photolysis of caged glutamate, 2) diffusion of released glutamates in extracellular region, 3) binding of glutamate to various receptors, such as AMPA and NMDA, on postsynaptic membrane surface, and finally 4) facilitation of excitatory postsynaptic potential to derive the action potential. First, using empirical results, we estimated the amount of photo-released glutamate, which allowed us to calculate the amount of uncaged glutamate, given the concentration of caged glutamate, the intensity and wavelength of light source, and the duration of illumination. Second, to cope with the demanding computational complexity due to the multiple sources of randomness, we use the adiabatic approximation, in which the time scale of molecular diffusion is sufficiently short compared to the neuronal activation. Under this approximation, the released neurotransmitter molecules are considered in diffusive equilibrium and the opening of postsynaptic ion channels can be calculated as a function of extracellular glutamate concentration. In the light of these considerations, we developed a multi-compartment model incorporating the manipulated extracellular glutamate concentrations and postsynaptic current combined, which will find use not only in the analysis of experimental results but also in the rational design for photolysis-induced neuronal stimulation experiments.

Disclosures: **H. Yang:** None. **J. Lee:** None. **G. Choi:** None. **W. Jung:** None. **C. Ghim:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

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Program#/Poster#: 175.24/UU76

Topic: I.03. Anatomical Methods

Support: MRC MC_UP_1201/2

ERC STG 677029

Title: Life-long genetic and functional access to neural circuits using self-inactivating Rabies virus

Authors: ***E. CIABATTI**, A. GONZÁLEZ-RUEDA, L. MARIOTTI, F. MORGESE, M. TRIPODI
MRC Lab. of Mol. Biol., Cambridge, United Kingdom

Abstract: Neural networks are emerging as the fundamental computational unit of the brain and it is becoming progressively clearer that network dysfunction is at the core of several psychiatric and neurodegenerative disorders (Rubinov and Bullmore, 2013; Roselli and Caroni, 2012). Yet, our ability to target specific networks for functional or genetic manipulations remains limited. Monosynaptically restricted G-deleted Rabies virus (ΔG-Rabies, Wickersham et al., 2007)

facilitates the investigation of neural circuits' structure by the selective label of first-order presynaptic partners. However, despite the transformative role of ΔG-Rabies based approaches in defining the anatomical organization of neuronal circuits, its implementation in long-term functional studies and for the genetic manipulation of neural networks is largely prevented by the Rabies virus inherent cytotoxicity. To overcome this limitation, we engineered the Rabies virus genome so to completely eliminate its toxicity. We generated a Self-inactivating ΔG-Rabies virus (SiR) that provides permanent life-long genetic access to neural circuits. We show that SiR infected neurons retain unaltered physiological properties, functional connectivity and normal synaptic function for the entire life of the animal. Furthermore, we used SiR to perform *in vivo* 2-photon calcium imaging of V1 neurons projecting to V2, showing that computational properties of V1 neurons, such as their orientation tuning, remain intact after SiR infection for unbounded periods of time. The development of the SiR virus gives, for the first time, permanent genetic access to neural networks with no adverse effects on neural physiology, circuit function and circuit-dependent computations. This opens new horizons in the functional investigation of neural circuits and potentially represent the first approach to experimentally follows neural circuits remodelling *in vivo*.

Disclosures: E. Ciabatti: None. **A. González-Rueda:** None. **L. Mariotti:** None. **F. Morgese:** None. **M. Tripodi:** None.

Poster

175. Connectomics: Automatic Tracing Techniques

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Program#/Poster#: 175.25/UU77

Topic: I.03. Anatomical Methods

Support: NIH Grant EY024844

Title: Neuronal connectivity analysis in zebrafish with monosynaptic viral labeling and 3D mapping

Authors: *M. M. MA, S. KLER, Y.-C. A. PAN
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Abstract: The combination of small size, translucency, and powerful genetics makes larval zebrafish an ideal vertebrate system to investigate normal and pathological brain functions. However, it remains challenging to map out the myriad of connections between neurons and identify cellular level connectivity changes during development or disease. We previously found that vesicular stomatitis virus (VSV) can effectively infect zebrafish neurons and label connected neurons, paving the way for rapid brain mapping (*J Comp Neurol.* 2015; 523:1639-63). In the current study, we aim to develop a new VSV-based approach that can (1) target specific cell

types, (2) limit spread to monosynaptic, and (3) quantitatively describe the spatial distribution of postsynaptic cells. We achieved these goals by (1) utilizing the EnvA-TvA cell-targeting system, (2) making synaptic spread dependent on helper virus, and (3) integrate image analysis with an annotated zebrafish 3D brain atlas (Z-Brain, *Nat Methods*. 2015 11:1039-46). Our method identified retinorecipient cells near the optic tract terminals in the hypothalamus, thalamus, pretectum and the optic tectum, consistent with previous studies. The location of retinorecipient cells was mapped and measured in Z-Brain and divided into GABA+ (inhibitory) and GABA- (excitatory) groups. In addition, due to the sparsity of labeling, we were able to clearly identify different types of retinorecipient projection neurons and trace their axon trajectory. Work is currently in progress to engineer VSV for more efficient spread, improved host cell health, and to identify abnormal connectivity patterns in zebrafish models of neurological and psychiatric diseases.

Disclosures: M.M. Ma: None. **S. Kler:** None. **Y.A. Pan:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.01/UU78

Topic: I.06. Computation, Modeling, and Simulation

Title: The zero lag time in manual tracking performance

Authors: *H. U. VOSS
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Abstract: Objectives
Manual time-delayed feedback tracking of continuously moving targets has been shown to be controlled by a simple filter with anticipatory coupling that involves a time delayed feedback [1]. This model explains the observations that for small feedback times subjects lag, and for larger feedback times lead, the target [2]. The amount of lag or lead is determined by the filter's group delay, which is positive for lagging and negative for leading dynamics, with a continuous transition between both dynamics. The transition point follows from the feedback delay time. Therefore, there is a delay time for which tracking becomes accurate in the sense of zero average lag time, the 'zero lag time.' My objective is to show how the zero lag time can be estimated from non-time delayed feedback tracking, and to demonstrate the feasibility of modifying human motor control performance by artificial delays.
Methods
In a feedback-delayed manual tracking experiment model [1] the lag/lead time of the subject's motion is
$\delta=(\tau_0-\tau)/2$,

where δ is the observed lag or lead time (positive for lag), τ the experimental feedback delay, and τ_0 the zero lag time. The latter is called as such because $\delta=0$ for $\tau=\tau_0$. Extrapolating this notion to non-feedback delayed tracking ($\tau=0$), τ_0 can be estimated as
$\tau_0=2\delta$.
It follows that approximately zero lead/lag ($\delta\approx0$) should be expected under two alternatives:
1. The manual tracking experiment is feedback-delayed with delay $\tau=\tau_0$. This is the strategy pursued here.
2. The subject's coordinates are predicted in real time by a negative group delay filter [3] with group delay $-\tau_0/2$.

Results

Matlab tracking algorithms are available for research from the author per email. A test with random trajectories [3] resulted in a lag time for manual tracking without feedback of 90 ms, or zero lag time of $\tau_0 = 180$ ms. Three runs with feedback delay τ_0 yielded horizontal/vertical-averaged group delays of -40, 0, and -20 ms, a clear improvement over the 90 ms lag achieved without feedback enhancement.

Discussion

This approach of motor control modification might be useful in applications of motor prosthetics and man-machine interface applications, for example to compensate timing
errors in assisted motion. The mechanism is reminiscent of delayed-leak integrators [4] and the observed lag/lead transition in a simple neuronal motif [5].

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[3] H.U. Voss, Phys Rev E **93**, (2016).
[4] H.U. Voss, Neural Comput. **28**, 1498 (2016).
[5] F.S. Matias et al., Phys Rev E **84**, (2011).

Disclosures: H.U. Voss: None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.02/UU79

Topic: I.06. Computation, Modeling, and Simulation

Support: NIH-MH60163

T32 NS058280-04S1

Title: Motor temporal scaling reveals a novel interaction between speed and timing reliability

Authors: *N. HARDY[1], V. GOUDAR[1], J. ROMERO-SOSA[2], D. V. BUONOMANO[3]
[1]Neurobio., [3]Dept Neurobiol, [2]UCLA, Los Angeles, CA

Abstract: Timing is fundamental to complex motor behaviors: activities from tying a knot to playing the piano require complex spatiotemporal patterns of neural activity. One intriguing aspect of motor timing is related to how we produce similar motor patterns at different speeds. We can generate well-trained motor behaviors such as tying a shoe or writing your name can at different speeds with little extra effort. Despite the importance and universality of temporal scaling in the motor domain, basic questions on both the psychophysical and computational levels remain unaddressed. For example, is temporal scaling intrinsic to motor timing?
Here we report that temporal scaling is not innate to either human behavior or network dynamics. After learning to tap the Morse code for "time" at 10 words per minute, subjects were unable to accurately reproduce the pattern at novel speeds, with accuracy decreasing the further subjects were from the trained speed. To examine the network mechanisms behind temporal scaling, we turned to a recurrent neural network model (RNNs). Initial studies showed that RNNs also do not inherently scale their activity: altered input drive not only failed to change the speed of the dynamics, but degraded performance at more extreme levels.
However, we go on to show that RNNs can be trained to produce robust temporal scaling. Networks trained to produce a pattern of aperiodic "taps" at multiple speeds were able to accurately generalize their activity to untrained speeds. Further, the model captures a signature of motor timing—Weber's law—but predicts that timing will be more precise at faster speeds. To test this prediction, humans were asked to produce a continuous motor pattern of six taps at multiple speeds, replicating the output of the RNN. However, unlike in the previous Morse code task, subjects were cued with the correct target speed. Analysis of the timing of the taps revealed the standard deviation of a response at a given absolute time was lower for faster speeds. These results establish for the first time that RNNs can account for temporal scaling, and that Weber's law is speed-dependent.

Disclosures: N. Hardy: None. **V. Goudar:** None. **J. Romero-Sosa:** None. **D.V. Buonomano:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.03/UU80

Topic: I.06. Computation, Modeling, and Simulation

Support: ADHE SURF award

Title: High fidelity information transmission comes at the cost of compromised stimulus discrimination

Authors: *K. L. MCCLANAHAN, W. L. SHEW
Univ. of Arkansas, Fayetteville, AR

Abstract: In general, sensory cortex is organized into hierarchical stages with primary sensory regions receiving input from subcortical regions and downstream, associative regions receiving input from primary regions. Two essential functional properties for such multi-region sensory systems are 1) the ability to discriminate different sensory input and 2) propagation of information from one region to another. Here we use a computational network-level model to study how discrimination and propagation of information are related in simple two-region systems. We consider one 'primary' region that receives external input and one 'associative' region that receives input from the 'primary' region. We ask, how should excitatory interactions in these networks be tuned to optimize discrimination of two similar input stimuli. First, we found that weak excitation optimized discrimination in the primary region. Such weak connectivity results in an asynchronous, subcritical dynamical regime with a low firing rate. However, weak excitatory connections compromise the efficacy of propagation from the primary to the association region. Thus, optimizing discrimination in the primary region results in sub-optimal discrimination in the association region. Conversely, optimizing discrimination in the association region requires somewhat suboptimal, stronger excitatory interactions in the primary region. This increase in excitatory interactions results in a shift towards criticality, the tipping point between asynchronous and synchronous firing. Our results suggest that, although subcritical dynamics may be optimal for single-network discrimination, multiple interacting networks may require a shift back towards critical dynamics for optimal discrimination.

Disclosures: K.L. McClanahan: None. **W.L. Shew:** A. Employment/Salary (full or part-time):; University of Arkansas.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.04/UU81

Topic: I.06. Computation, Modeling, and Simulation

Support: NSF Grant #1358567

Title: Comparing information-theoretic measures of complexity in Boltzmann machines

Authors: *M. S. KANWAL
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Abstract: In the past three decades, many theoretical measures of complexity have been proposed to help understand complex systems. In this work, for the first time we place these

measures on a level playing field, to explore the qualitative similarities and differences between them. Specifically, using the Boltzmann machine architecture (a fully connected recurrent neural network) with uniformly distributed weights as our model of study, we measure how complexity changes as a function of network dynamics and network parameters. We apply an extension of one such information-theoretic measure of complexity to understand incremental Hebbian learning in Hopfield networks, a fully recurrent architecture model of autoassociative memory. In the course of Hebbian learning, the total information flow reflects a natural upward trend in complexity, as the network attempts to learn more and more patterns.

Disclosures: M.S. Kanwal: None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.05/UU82

Topic: I.06. Computation, Modeling, and Simulation

Title: Optimal E:I cell ratios in efficient coding models of V1 under volume constraints

Authors: A. ALREJA[1], I. NEMENMAN[2], *C. ROZELL[3]
[1]Ctr. For Neural Cognition, Carnegie Mellon Univ., Pittsburgh, PA; [2]Emory Univ., Atlanta, GA; [3]Georgia Inst. of Technol., Atlanta, GA

Abstract: The inhibitory interneuron population plays an important role in shaping cortical activity but much remains unclear about its specific role in neural coding. While some theoretical models postulate the need for balanced excitatory and inhibitory activity, we lack an understanding of why cortical E:I cell ratios in different species are consistently in a range from 2:1-9:1. Understanding the principles underlying E:I ratios may help illuminate the role of inhibition in cortical circuits. Recent efficient coding models of vision include explicit inhibitory interneurons with biologically observed E:I ratios and interneuron tuning properties. While similar models show that increasing the number of excitatory and inhibitory cells improves the quality of stimulus representation, current models do not account for the fact that volume is a heavily constrained resource. Though both excitatory and inhibitory cell types are valuable for neural coding, a fixed volume constraint means that increasing the size of one neural subpopulation necessitates decreasing the size of the other.
We implement an efficient coding model of vision under a volume constraint that fixes the total population size while varying the E:I ratio. We show that the quality of the stimulus representation is optimal at biologically observed E:I ratios, which can be interpreted as balancing the trade-off between computational accuracy and representation capacity for natural stimuli. This potentially provides a normative account for observed cell type distributions in sensory cortex as optimizing coding fidelity under a volume constraint. Further, our model

suggests that specific optimal E:I ratios within biophysically observed ranges are proportional to population sparsity, with higher optimal E:I ratios observed for sparser population activity. This prediction is supported by recent electrophysiology recordings of large populations in V1 under natural scene stimuli for multiple species.

Disclosures: A. Alreja: None. **I. Nemenman:** None. **C. Rozell:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.06/UU83

Topic: I.06. Computation, Modeling, and Simulation

Title: Emergent spatio-temporal trade-off in axon arbors defines dynamic efficiency in neurons

Authors: *F. PUPPO, V. GEORGE, G. A. SILVA
Bioengineering, UC San Diego, La Jolla, CA

Abstract: The brain is a complex network of individual branching axons that ensure rapid and efficient communication between billions of connected neurons. Despite recent advancements, it remains unclear how such a highly-interconnected system optimizes the processing of information and what is the role of the morphology of individual axons and axonal arborizations in defining signaling efficiency. Contrarily to the predominant view that wiring minimization principles are sufficient to understand neuronal organization, neurons are neither optimized to minimize the wiring path length of axons nor to maximize conduction velocities. Here we show an analysis supporting the hypothesis that axon arbors are designed according to a fundamental principle based on the conservation and optimization of a tradeoff between the time it takes a signal to reach postsynaptic targets (temporal cost), which is a function of the wiring length of the axon (material cost), and the refractory properties of the membrane, which limit how quickly incoming signals can be manipulated by the neuron.We have developed a novel mathematical framework to analyze the spatio-temporal evolution of signaling in geometric networks consisting of morphologically reconstructed axons represented as directed tree graphs. The signaling efficiency ratio represents the numerical ratio between signaling latency, determined by the geometry of the network and biophysics of the membrane, and the internal processing time of individual nodes, that is a function of the membrane refractoriness. We use it as a parameter to analyze information flow patterns in the network. The outcome of our study shows signaling ratios approaching values that we have mathematically shown to represent the theoretical limits of optimal signaling efficiency. Therefore, it demonstrates not only the key role of the arbor topology in preserving an optimal spatio-temporal balance required for optimal signaling, but also that the signaling ratio is the cost function that neurons actively optimize to achieve it.Finally, we propose that a similar analysis can be used to investigate functional changes

associated with neurodevelopmental disorders, in particular Autism Spectrum Disorder, that putatively alter the communication efficiency of neurons. In this context, our analysis represents a powerful and unique approach for analyzing fMRI and EEG data that can identify dynamic breakdowns and deviations in signaling between connected brain regions in patients and which can potentially be used as an optimization parameter for perturbation methods such as transcranial magnetic stimulation (TMS) and related approaches.

Disclosures: F. Puppo: None. **V. George:** None. **G.A. Silva:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

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Program#/Poster#: 176.07/VV1

Topic: I.06. Computation, Modeling, and Simulation

Support: ERC Starting Grant No. 716643

Title: Getting good predictions from bad neuron models

Authors: D. RAMAN, *T. O'LEARY
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Computational models offer a way to understand nervous system function, but constraining models with experimental data is very challenging. Most models are extremely complex, with many free parameters, and data are often noisy or incomplete [1, 2]. Worse still, a model itself is likely to be wrong. For example, a network model may have different connectivity to the biology, or conductance-based models of a neuron may miss specific conductances or have incorrect kinetics. We show that incorrect models can nonetheless give useful predictions and replicate dynamics of the system to which they are fitted. However, the predictive power and robustness of parameter estimates critically depend on the choice of error metric used to constrain the model [3]. We introduce an error metric that captures the input-output behavior of a conductance-based model and show that fitting with this metric can produce more qualitatively realistic predictions than with the traditional mean squared error between data and model. Moreover, the two different error metric give very different estimates of model sensitivity to changes in parameters. For our metric, we introduce a method of computing both the model error and its gradient with respect to parameters, which does not require simulation of the model differential equations. This reduces the computational difficulty of parameter estimation by an order of magnitude. These results show that the predictive power of data-driven models crucially depends on the ability to obtain experimental data with known perturbations.
References: [1] O'Leary, T., Sutton, A. C., & Marder, E. (2015). Computational models in the age of large datasets. Current opinion in neurobiology, 32, 87-94. [2] Achard, P., & De Schutter,

E. (2006). Complex parameter landscape for a complex neuron model. PLoS Comput Biol, 2(7), e94. [3] Druckmann, S., Berger, T. K., Hill, S., Schürmann, F., Markram, H., & Segev, I. (2008). Evaluating automated parameter constraining procedures of neuron models by experimental and surrogate data. Biological cybernetics, 99(4), 371-379.

Disclosures: D. Raman: None. **T. O'Leary:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.08/VV2

Topic: I.06. Computation, Modeling, and Simulation

Title: Measures of integration and differentiation in microscale model networks: Computationally feasible PHI correlates

Authors: *A. S. NILSEN[1], B. E. JUEL[2], J. F. STORM[3]
[1]Brain signalling group, Univ. of Oslo, Oslo, Norway; [2]Inst. of Basic Med. Sci., [3]Univ. of Oslo, Oslo, Norway

Abstract: Introduction: Integrated information theory (IIT) developed by Guilio Tononi (2014) proposes a method to calculate the quantity of the maximally irreducible conceptual structure (MICS) of a system in a given state, termed phi (Φ). Phi, according to the IIT, is a measure of a system's capacity for consciousness. Unfortunately, to calculate phi you need the full state transition matrix of the system. In addition you need to find the largest MICS for a given system, requiring you to iterate over all possible partitions of the system. Thus, calculating phi is realistically impossible for systems of interest such as brains or computers. We aim to test analogues to phi that are more practical in terms of pre-conditions and less computationally expensive, and compare them directly to phi in model systems.
Methods: We modeled randomized networks of 3-6 nodes in the Neural Simulator Tool (NEST) consisting of integrate and fire neurons with an alpha function, tuned so to approximate binary behavior, with the possibility of inhibitory synapses. We perturbed these systems into all possible states and measured the following spike patterns. Then we calculated phi of the whole system for each state and phi of each state's main complex, two measures based on state differentiation and state entropy, several measures based on number of activated states during natural conditions, as well as several signal complexity measures based on Lempel Ziv complexity.
Results: Preliminary findings suggest that phi of the whole system in a state closely correlates with that of its main complex, and that the average phi of the whole system over all states is strongly correlated with the system's highest phi state. We also observed that the average number of states and Lempel Ziv complexity in a given section of the state transformation matrix

and a measure of overall state differentiation has medium to strong correlation with average phi for that system's states.
Conclusion: Our findings suggest that calculating the average phi over the whole system for a subset of states closely approximates the quantity of the MICS (main complex) for the maximally integrated state. This can possibly save computational time when estimating phi for smaller systems. We also observe that measures of complexity, state differentiation, and number of naturally occurring states, might moderately reflect phi. However, although these measures are also practically infeasible in large scale networks due to limits in the spatial resolution of current technology, they are computationally efficient relative to phi.

Disclosures: **A.S. Nilsen:** None. **B.E. Juel:** None. **J.F. Storm:** None.

Poster

176. Neurocomputational Limits

Location: Halls A-C

Time: Sunday, November 12, 2017, 8:00 AM - 12:00 PM

Program#/Poster#: 176.09/VV3

Topic: I.06. Computation, Modeling, and Simulation

Title: How strong are correlations in strongly recurrent networks?

Authors: *R. DARSHAN[1], C. VAN VREESWIJK[2], D. HANSEL[2]
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Abstract: Measuring cross-correlations (CCs) is a standard way to characterize the spatiotemporal organization of the activity of neural networks in the brain. Information theoretic considerations indicate that the computations a network can perform are strongly affected by the strength of the CCs. Experiments revealed that CCs vary in a broad range of strengths, depending on animals, brain states, brain areas or within layers of the same cortical area. Understanding what determines the strength of CCs is thus a fundamental theoretical and experimental issue. Previous theoretical studies showed that in strongly recurrent but unstructured networks correlations are extremely small: their average scales in inverse proportion to the network size [Renart 10'; Helias et al. 14']. Recently, we showed that the interplay between feedforward and spatially structured recurrent interactions may increase dramatically the strength of correlations [Darshan et al. 17']. Here, we develop a general theory of correlations in strongly recurrent networks. We combine analytical proofs and numerical simulations to establish the general constraints on the architecture of networks for strong correlations (proportional to the density of the connectivity) to emerge from its dynamics. We then characterize how the correlations depend on the connectivity and how strong they can be when these conditions are not met. Finally, we discuss how the stability of the correlated state depends on the connectivity.

Disclosures: **R. Darshan:** None. **C. van Vreeswijk:** None. **D. Hansel:** None.

Poster

176. Neurocomputational Limits

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Topic: I.06. Computation, Modeling, and Simulation

Support: AFOSR Grant FA9550-12- 10232

NSF Grant 1544383

Title: A general model for divisive normalization and its identification

Authors: *N. UKANI, Y. ZHOU, A. LAZAR
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Abstract: Divisive normalization has been proposed as a canonical computation performed by neural circuits [1] and it is believed to occur across different sensory modalities and species. This computation is key to many sensory processing circuits underlying attention and adaptation, yet there is a lack of general mathematical framework to identify such computations from recorded data.

We propose a general model for divisive normalization whose output is determined by the ratio between the outputs of two nonlinear functionals. For the sake of tractability, we limit each functional to be composed of a linear filter and a second-order nonlinear filter. The ratio of the two functionals allows us, however, to model nonlinear processing of much higher orders. By imposing appropriate low-rank constraints on the second-order filters, we provide tractable algorithms for identifying both temporal and spatio-temporal filters.

We evaluated our identification algorithm on a number of cases. First, we tested a large number of synthetically generated divisive normalization models and empirically demonstrated that the implemented algorithm, with enough measurements, exactly identified the original filters with high probability. We then applied the algorithm to identify 1) spatiotemporal filters involved in the phase-based motion detection model [2] and showed that the quality of identification reached an average SNR of ~45 [dB] for all filters in the system (see Fig. 1), and 2) a phenomenological equivalent of a detailed biophysically realistic model of *Drosophila* photoreceptors [3] and demonstrated that the responses of the identified divisive normalization model to novel stimuli match those of the original model.

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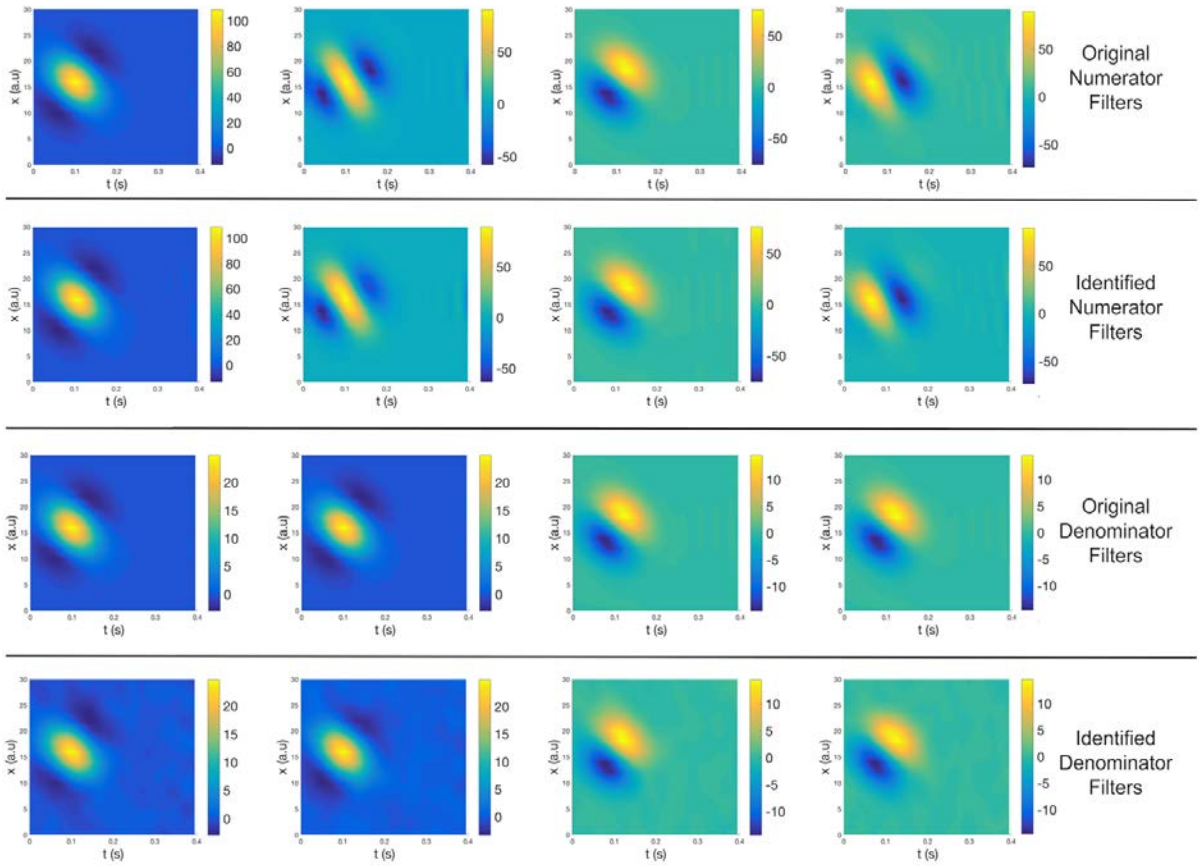

Figure 1: Original and identified spatiotemporal filters for the phase based motion detection model.

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